



(11) Publication number : **0 573 271 A1**

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number : 93304264.0

(22) Date of filing : 02.06.93

(51) Int. Cl.⁵ : **C07D 233/88, C07D 401/06, C07D 401/14, C07D 403/06, C07D 403/14, C07D 405/14, C07D 409/14, C07D 413/14, A61K 31/41**

(30) Priority : 03.06.92 US 892867
20.04.93 US 49917

(43) Date of publication of application :
08.12.93 Bulletin 93/49

(84) Designated Contracting States :
AT BE CH DE DK ES FR GB GR IE IT LI LU NL
PT SE

(71) Applicant : **ELI LILLY AND COMPANY**
Lilly Corporate Center
Indianapolis Indiana 46285 (US)

(72) Inventor : **Boyd, Donald Bradford**
645 Lawnwood Drive
Greenwood, Indiana 46142 (US)
Inventor : **Hauser, Kenneth Lee**
700 Kirkwood Drive
Greencastle, Indiana 46135 (US)
Inventor : **Lifer, Sherry Lynn**
844 Sunbow Circle
Indianapolis, Indiana 46231 (US)
Inventor : **Marshall, Winston Stanley**
16 Briar Patch Road
Bargersville, Indiana 46106 (US)

Inventor : **Palkowitz, Alan David**
2341 Springside Lane North
No.C Indianapolis, Indiana 46260 (US)

Inventor : **Pfeifer, William**
1402 Oakwood Trail
Indianapolis, Indiana 46260 (US)

Inventor : **Reel, Jon Kevin**

14701 Alsong Court

Carmel, Indiana 46032 (US)

Inventor : **Simon, Richard Lee**

371 Redbud Place

Greenwood, Indiana 46142 (US)

Inventor : **Steinberg, Mitchell Irvin**

932 Roundtable Court

Indianapolis, Indiana 46260 (US)

Inventor : **Takeuchi, Kumiko**

8856 Doral East Drive, Apartment C

Indianapolis, Indiana 46250 (US)

Inventor : **Thrasher, Kenneth Jeff**

8660 Count Turf Court

Indianapolis Indiana 46217 (US)

Inventor : **Whitesitt, Cella Ann**

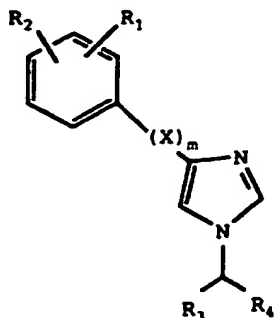
4089 Easy Street

Greenwood, Indiana 46142 (US)

(74) Representative : **Hudson, Christopher Mark et al**
Erl Wood Manor
Windlesham Surrey GU20 6PH (GB)

(54) **Angiotensin II antagonists.**

(57) This invention provides pharmaceutical phenyl and heterocyclic derivatives of the formula



(I)

EP 0 573 271 A1

EP 0 573 271 A1

They antagonize angiotensin II receptors in mammals.

The hormone angiotensin II is recognized as one of the most potent vasopressor agents that produces hypertension in mammals. The action of the enzyme renin on the plasma protein substrate angiotensinogen results in the production of an inactive decapeptide, angiotensin I, which upon conversion by the nonselective selective angiotensin converting enzyme (ACE) provides angiotensin II, the active hormone. See, e.g., Regoli et al., *Pharm. Rev.*, **26**, 69 (1974).

Angiotensin II causes vasoconstriction and stimulates aldosterone secretion (from the adrenal gland) that results in a rise of both blood volume and pressure. Inhibitors of angiotensin II are therefore useful in treating hypertension, congestive heart failure, renal insufficiency associated with diabetic or hypertensive nephropathy, and glaucoma. See Garrison et al., in *The Pharmacological Basis of Therapeutics*, 8th Edition, Eds. A. G. Gilman, E. S. Goodman, T. W. Rall, A. S. Nies, and P. Taylor, Pergamon Press, New York, 1990: p. 761-762; and Dzau V. J., *The New Eng. J. Med.* **324**: 1124-1130 (1991).

Angiotensin II also can act on other organs such as the brain (Fitzsimmons, *Rev. Physiol. Biochem. Pharmacol.*, **87**, 117, (1980)). Antagonists of angiotensin II are therefore useful in enhancing cognitive performance in patients affected by conditions such as age associated mental impairment or Alzheimer's disease and in treating cognitive disorders such as anxiety. See Dennes et al., *Brit. J. Pharmacol.* **105**: 88p (April 1992); and Barnes, J. M., et al., *FASEB J.* **5**: 678 (March 1991).

In addition, angiotensin II acts on a variety of glandular tissues including the kidney, liver, and ovaries. Antagonists of angiotensin II are useful in treating conditions, disorders, or diseases of these tissues associated with excessive or unregulated angiotensin II activity. Antagonists of angiotensin II are also useful in treating kidney damage due to nonsteroidal antiinflammatory agents.

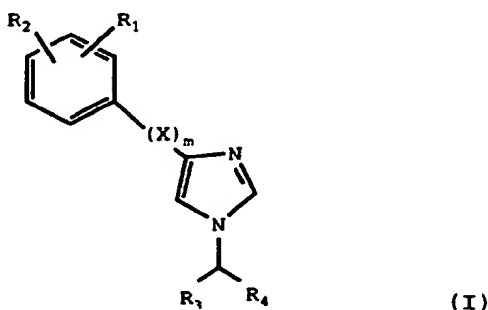
Angiotensin II has a role in regulation of the rate of cell growth and differentiation. Inhibitors of angiotensin II are therefore useful in treating disorders marked by excessive cell proliferation such as restenosis.

See, e.g., Naftilan et al., *J. Clin. Invest.* **83**, 1419 (1989), Kauffman et al., *Life Sciences*, **49**: 223-228 (1991), and Jackson et al., *Nature*, **335**, 437 (1988).

Some antihypertensive agents act as inhibitors of ACE thus blocking the formation of angiotensin II and its resulting increase of blood pressure. More recently, both peptide and nonpeptide receptor antagonists of angiotensin II have been disclosed — see, e.g., EPO Patent Application Publication 253310 and references contained therein, and Chiu et al., *J. Pharmacol. Exp. Ther.*, **250**, 867 (1989). Although peptide antagonists have had an important role in uncovering the physiological roles for Angiotensin II, their therapeutic usefulness was ultimately limited by either partial agonist activity, metabolic instability or both. See Ashworth R.W. *Birkhäuser Verlag* **26** (1982).

The present invention provides novel, potent, and effective compounds that antagonize angiotensin II at receptor sites in the body and are therefore useful in treating conditions associated with excessive or unregulated angiotensin II activity such as hypertension, congestive heart failure, cognitive disorders, renal insufficiency associated with diabetic or hypertensive nephropathy, glaucoma, kidney damage due to nonsteroidal antiinflammatory agents, and restenosis.

This invention provides compounds of Formula I



and pharmaceutically acceptable salts or solvates thereof wherein:

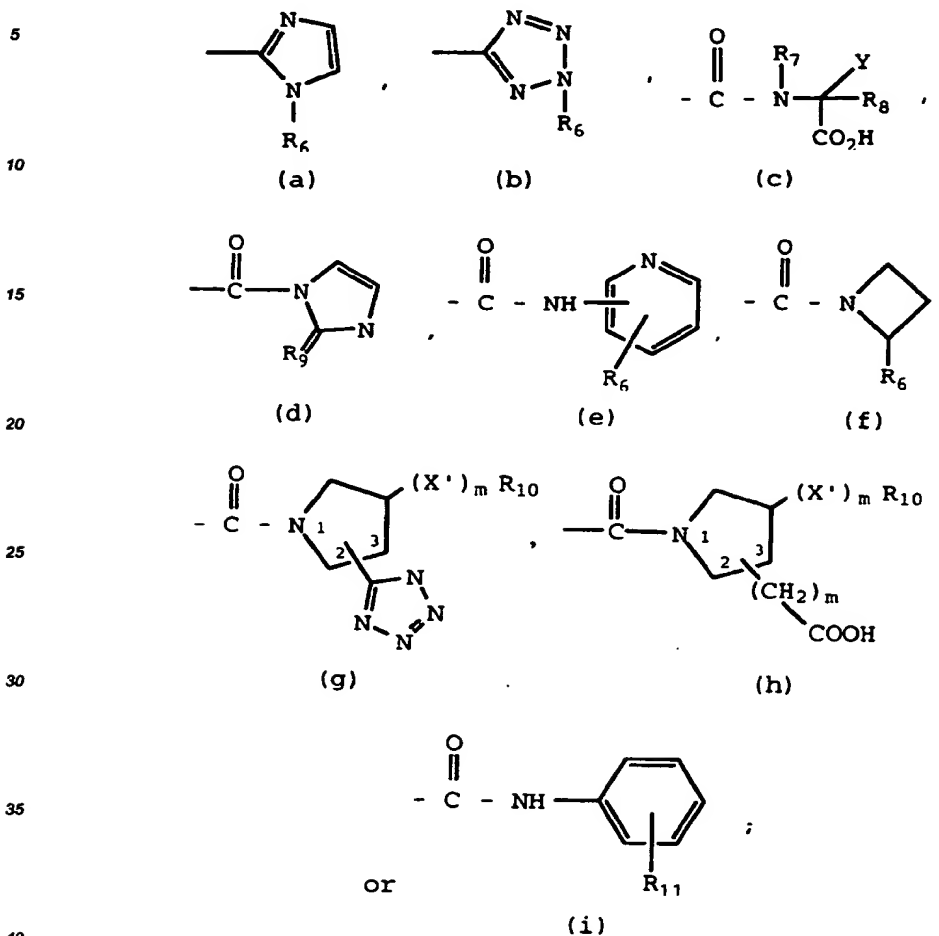
R₁ is CO₂H, SO₃H, PO₃H₂, CONHSO₂R₆ or 5-tetrazolyl;

R₂ is H, -OH, -OCOCH₃, halo, C₁-C₄ alkyl, amino, acetamido, or C₁-C₄ alkoxy;

X is -(CH₂)_mNHCO-, -(CH₂)_mCONH-, -O-, -NH-, -CH₂-, -(CH₂)_mCO-, or -CO(CH₂)_m-;

R₃ is C₄-C₉ straight chain alkyl, C₄-C₉ straight chain trifluoroalkyl, C₄-C₉ straight chain alkenyl, or C₄-C₉ straight chain trifluoroalkenyl;

R_4 is $-\text{CONH}(\text{C}_1\text{-C}_4 \text{ alkyl})$, $-\text{CONH}(\text{C}_1\text{-C}_4 \text{ trifluoroalkyl})$, $-\text{CONH}(\text{hydroxy-C}_1\text{-C}_4 \text{ alkyl})$,



R_6 is phenyl, $\text{C}_1\text{-C}_4$ alkyl substituted phenyl, $\text{C}_1\text{-C}_6$ alkyl, or $\text{C}_1\text{-C}_6$ trifluoroalkyl;

R_8 is $(\text{CH}_2)_p\text{R}_1$, or $\text{C}_1\text{-C}_4$ alkyl;

R_7 is H or CH_3 ;

R_9 is H or $-(\text{CH}_2)_q\text{R}_{12}$;

R_9 is O or S;

R_{10} is H, $-(\text{CH}_2)_p\text{R}_1$, $\text{C}_1\text{-C}_7$ alkyl, $\text{C}_1\text{-C}_7$ trifluoroalkyl, halo, substituted or unsubstituted phenyl, 3-pyridyl, 2-pyrimidyl, furanyl, oxazolyl, isoxazolyl, a substituted or unsubstituted fused bicyclic, a substituted or unsubstituted fused tricyclic, or when m is 0, 4,4-ethylenedioxy;

R_{11} is H, OH, $\text{C}_1\text{-C}_4$ alkoxy, CO_2H , SO_3H , PO_3H_2 , $\text{CONHSO}_2\text{R}_6$, or tetrazolyl;

R_{12} is OH, NH_2 , or CO_2H ;

Y is a R group of a naturally occurring amino acid;

X' is $-\text{O}-$, $-(\text{CH}_2)_p-$, or $-\text{S}-$;

m is independently 0 or 1;

p is independently 0, 1, 2, 3 or 4; and

q is 1, 2, 3, or 4;

providing that when R_4 is (g) or (h), and R_{10} is not H, the carboxy of (h) or tetrazolyl of (g) is in position 2; and when R_4 is (g) or (h), m is 0, and R_{10} is H, the carboxy of (g) or tetrazolyl of (h) is in position 2 or 3; and a pharmaceutically acceptable salt or solvat thereof.

This invention also provides a method for treating hypertension which comprises administering to a mammal in need of such treatment an antihypertensive amount of a compound of the Formula I.

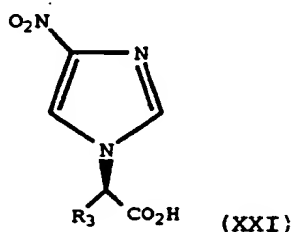
5 This invention further provides methods for treating congestive heart failure, renal insufficiency associated with hypertensive or diabetic nephropathy, restenosis, kidney damage due to nonsteroidal antiinflammatory agents, anxiety, and glaucoma which comprise administering to a mammal in need of treatment a pharmaceutically effective amount of a compound of the Formula I.

10 A further aspect of the present invention is a method of enhancing cognitive performance which comprises administering to a mammal in need of enhancement a pharmaceutically effective amount of a compound of the Formula I.

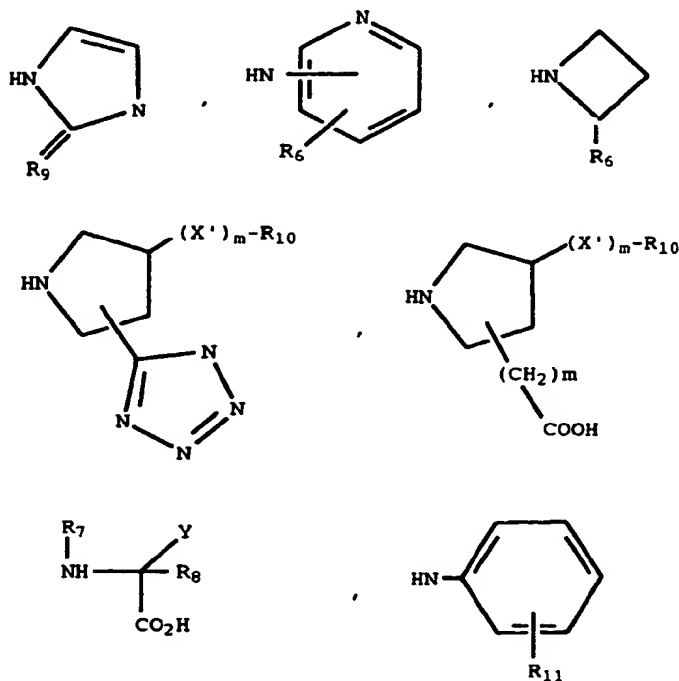
Also provided are pharmaceutical formulations comprising a compound of Formula I together with one or more pharmaceutically acceptable excipients, carriers, or diluents.

An additional aspect of this invention is a process of preparing the preferred stereoisomer of Formula I, comprising:

15 coupling a compound of the formula (XXI)

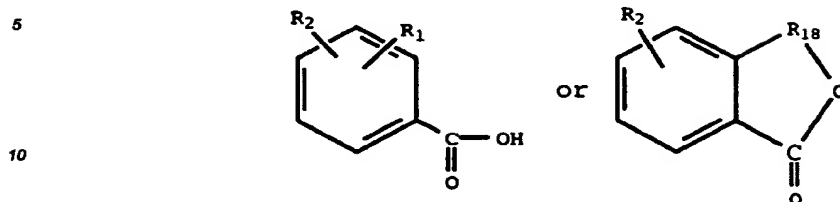


wherein R₃ is C₄-C₉ straight chain alkyl, C₄-C₉ straight chain trifluoroalkyl, C₄-C₉ straight chain alkenyl, or C₄-C₉ straight chain trifluoroalkenyl; to a compound of the formula:



wherein R₆, R₇, R₈, R₉, R₁₀, R₁₁, R₁₂, and Y are the same as previously defined;
reducing the nitro of the compound of the formula (XXI) to produce an amino imidazole;

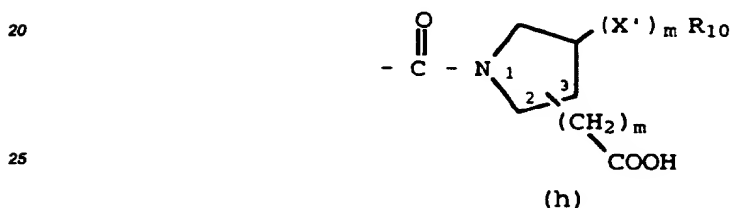
coupling the amino imidazole to a compound of the formula:



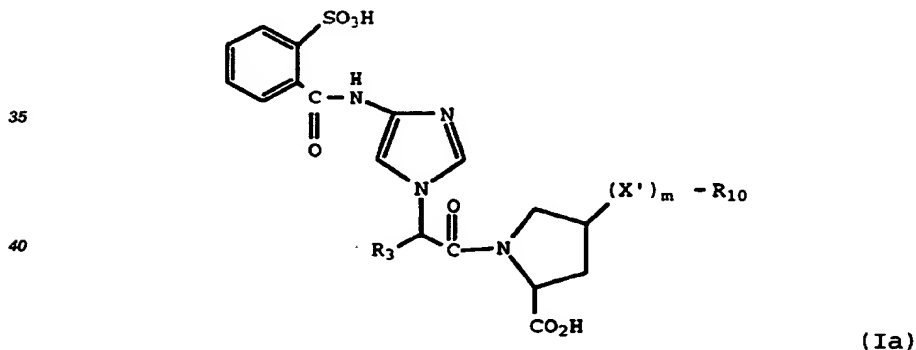
wherein R_2 and R_1 are the same as previously defined; R_{18} is SO_2 or C=O .

15 As noted above, the invention provides compounds of the Formula I which antagonize angiotensin II at the receptor sites in the body. The preferred compounds of this invention are those of Formula I wherein:

R_4 is



Particularly preferred compounds of this invention are those of Formula Ia:



45 wherein R_3 is a C_4 - C_9 straight chain alkyl; R_{10} is an unsubstituted or para substituted phenyl, a substituted or unsubstituted fused bicyclic, a substituted or unsubstituted fused tricyclic; m is 0 or 1; X' is $-\text{O}-$, $-\text{S}-$, or $(\text{CH}_2)_p$; and p is 0, 1, 2, 3 or 4.

50 Most preferred compounds are compounds in which X' is $-\text{O}-$, and R_{10} is a substituted phenyl of the formula:



wherein R_{13} is $-(\text{CH}_2)_p\text{R}_1$, $-\text{O}(\text{CH}_2)_p\text{R}_1$, $-\text{SO}_2\text{NR}_{14}\text{R}_{15}$, $-(\text{CH}_2)_p\text{CONR}_{14}\text{R}_{15}$, $-(\text{CH}_2)_p\text{NR}_{16}\text{SO}_2(\text{C}_1\text{-C}_4 \text{ alkyl or C}_1\text{-C}_4 \text{ trifluoroalkyl})$, or a heteroaryl selected from imidazolyl, triazolyl, tetrazolyl, thiazolyl, isoxazolyl, or oxazolyl,

said heteroaryl being optionally substituted with $-(CH_2)_pR_1$; R_{14} and R_{15} are independently H, C_{1-4} alkyl, $-(CH_2)_pCO_2H$ or taken together with nitrogen to which they are bonded constitute a heterocyclic ring selected from the groups consisting of pyrrolidino or piperidino, said heterocyclic ring being optionally substituted with $-COOH$; R_{16} is H or C_{1-4} alkyl.

Examples of the preferred compounds include the following:

1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-4-cis-(4-carboxyphenoxy)-L-proline
 1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-4-cis-(4-carboxymethylphenoxy)-L-proline
 1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-4-cis-(4-*t*-butoxyphenoxy)-L-proline
 1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-4-cis-(4-methylsulfonylphenoxy)-L-proline
 1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-4-cis-(5-benzofuranoxy)-L-proline
 1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-4-cis-(2-naphthoxy)-L-proline
 1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-4-cis-(4-carboxymethoxyphenoxy)-L-proline
 1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-4-cis-(2-carboxybenzofuran-5-yloxy)-L-proline
 1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-4-cis-((4-methylene phosphonic acid)-phenoxy)-L-proline

The terms " C_{1-4} alkyl," " C_{1-6} alkyl," " C_{1-7} alkyl," and " C_{1-9} alkyl" represent a cyclo, straight or branched chain alkyl group having from one to four, five, seven or nine carbon atoms respectively such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, sec-butyl, *t*-butyl, pentyl, isopentyl, 1-methylbutyl, 1-ethylpropyl, neopentyl, tert-pentyl, cyclopentyl, *n*-hexyl, isohexyl, 4-methyl hexyl, cyclohexyl, cyclohexyl methyl, *n*-heptyl, *t*-heptyl, iso-heptyl and the like.

The term "hydroxy- C_{1-4} alkyl" is a C_{1-4} alkyl substituted with a hydroxy. A hydroxy- C_{1-4} alkyl is preferably of the formula $HO(CH_2)_q$, where q is 1 to 4.

The terms " C_{1-4} trifluoroalkyl," " C_{1-6} trifluoroalkyl," and " C_{1-7} trifluoroalkyl" represent a straight or branched chain alkyl group having from one to four, five or seven carbon atoms respectively in which the primary carbon is substituted with fluorine.

The term " C_{4-9} straight chain alkyl" represents a straight chain alkyl group having from four to nine carbon atoms. Examples of a " C_{4-9} straight chain alkyl" include *n*-butyl, *n*-pentyl, *n*-hexyl, *n*-heptyl, *n*-octyl, and *n*-nonyl.

The term " C_{4-9} straight chain trifluoroalkyl" represents a C_{4-9} straight chain trifluoroalkyl group in which the primary carbon is substituted with fluorine.

The terms " C_{1-4} alkoxy" and " C_{1-7} alkoxy" represent a C_{1-4} or C_{1-7} alkyl group covalently bonded to the parent moiety by an -O- linkage.

The terms " C_{1-4} trifluoroalkoxy" and " C_{1-7} trifluoroalkoxy" represent a straight or branched chain C_{1-4} or C_{1-7} trifluoroalkyl group covalently bonded to the parent moiety by an -O- linkage.

The term " C_{4-9} straight chain alkenyl" represents a straight chain alkyl group having from four to nine carbon atoms and one double bond. Examples of a " C_{4-9} straight chain alkenyl" include *n*-butenyl, *n*-pentenyl, *n*-hexenyl, *n*-heptenyl, *n*-octenyl, and *n*-nonyl.

The term " C_{4-9} straight chain trifluoroalkenyl" represents a C_{4-9} straight chain alkenyl group in which the primary carbon atom is trisubstituted with fluorine. Examples of a " C_{4-9} straight chain trifluoroalkenyl" include 4-trifluoro-*n*-2-butenyl, 5-trifluoro-*n*-2-pentenyl, 6-trifluoro-*n*-3-hexenyl, 7-trifluoro-*n*-4-heptenyl, 8-trifluoro-*n*-6-octenyl, and 9-trifluoro-*n*-5-nonyl.

The term "R group of a naturally occurring amino acid" represents the variable region of the naturally occurring amino acids and is understood in the art. See, for example, Lehninger A. L. Biochemistry, 2nd edition, Worth Publishers, p. 73-75, 1975.

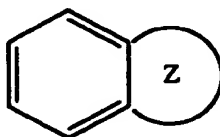
The term " $-(CH_2)_pR_1$ " represents a straight chain alkyl, branched alkyl, or a straight chain alkenyl bonded to R_1 or R_1 when p is zero. Examples of " $-(CH_2)_pR_1$ " include groups in which the straight chain alkyl, branched alkyl or straight chain alkenyl portion includes methylene, ethylene, trimethylene, tetramethylene, methylethylene, ethylethylene, 2-methyltrimethylene, ethenylene, propenylene, and butenylene.

The term "halo" includes fluoro, chloro, bromo, and iodo.

The term "substituted or unsubstituted phenyl" represents phenyl or phenyl substituted with one or more groups selected from $-(CH_2)_pR_1$, $-O(CH_2)_pR_1$, $-(CF_2)_pCO_2H$, C_{1-7} alkyl, C_{1-7} trifluoroalkyl, halo, $-(CH_2)_pOH$, cyano, phenylsulfonyl, phenyl, thiophenyl, thiocarboxy, C_{1-7} trifluoroalkoxy, C_{1-7} alkoxy, $-S(C_{1-4}$ alkyl), $-SO(C_{1-9}$ alkyl), $-SO_2(C_{1-9}$ alkyl), $-SO_2NR_{14}R_{15}$, $-(CH_2)_pCONR_{14}R_{15}$, $-(CH_2)_pNR_{16}SO_2(C_{1-4}$ alkyl or C_{1-4} trifluoroalkyl), or a heteroaryl selected from imidazolyl, triazolyl, tetrazolyl, thioazolyl, isoxazolyl, or oxazolyl, said heteroaryl being optionally substituted with $-(CH_2)_pR_1$; R_{14} and R_{15} are independently H, C_{1-4} alkyl, $-(CH_2)_pCO_2H$ or taken together with nitrogen to which they are bonded constitute a heterocyclic ring selected from the groups consisting of pyrrolidino or piperidino, said heterocyclic ring being optionally substituted with

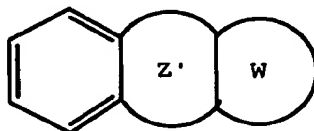
-COOH; R_{16} is H or C_1-C_4 alkyl. Preferably, a substituted or unsubstituted phenyl is a phenyl substituted with one substituent, preferably $-(CH_2)_pR_1$.

The term "fused bicyclic" represents a stable fused bicyclic ring system of the formula:



wherein Z represents a substituted or unsubstituted, saturated or unsaturated 5 or 6 membered ring, said ring having from zero to three heteroatoms that are the same or different and that are selected from the group consisting of sulfur, oxygen, and nitrogen; and when Z contains two adjacent carbon atoms, the adjacent carbon atoms may be structured to form a group of the formula $-CH=CH-CH=CH-$; provided that (1) when the heterocyclic ring contains 5 members, the heteroatoms comprise not more than one sulfur or two oxygen atoms but not both; (2) when the heterocyclic ring contains 6 members, sulfur and oxygen are not present; and (3) when the heterocyclic ring contains a sulfur or oxygen atom, the benzofusion is joined to a carbon adjacent to said sulfur or oxygen atom. The fused bicyclic may be attached at any carbon which affords a stable structure. The fused bicyclic may be substituted with one or two groups independently selected from $-(CH_2)_pR_1$, $-O(CH_2)_pR_1$, $-(CF_2)_pCO_2H$, C_1-C_7 alkyl, C_1-C_7 trifluoroalkyl, halo, $-(CH_2)_pOH$, cyano, phenylsulfonyl, phenyl, thiophenyl, thiocarboxy, C_1-C_7 trifluoroalkoxy, C_1-C_7 alkoxy, $-S(C_1-C_4 \text{ alkyl})$, $-SO(C_1-C_9 \text{ alkyl})$, $-SO_2(C_1-C_9 \text{ alkyl})$, $-SO_2NR_{14}R_{15}$, $-(CH_2)_pCONR_{14}R_{15}$, $-(CH_2)_pNR_{16}SO_2(C_1-C_4 \text{ alkyl or trifluoroalkyl})$, or a heteroaryl selected from imidazolyl, triazolyl, tetrazolyl, thiazolyl, isoxazolyl, or oxazolyl, said heteroaryl being optionally substituted with $-(CH_2)_pR_1$; R_{14} and R_{15} are independently H, C_1-C_4 alkyl, $-(CH_2)_pCO_2H$ or taken together with nitrogen to which they are bonded constitute a heterocyclic ring selected from the groups consisting of pyrrolidino or piperidino, said heterocyclic ring being optionally substituted with $-COOH$; R_{16} is H or C_1-C_4 alkyl.

The term "fused tricyclic" represents a stable fused tricyclic ring system of the formula:



wherein Z' represents a saturated or unsaturated 5 membered ring, said ring having zero or one heteroatom that is selected from the group consisting of sulfur, oxygen, and nitrogen; W represents a substituted or unsubstituted, saturated or unsaturated 6 membered ring, said ring having from zero to three nitrogen atoms. The fused tricyclic may be attached at any carbon which affords a stable structure. The fused tricyclic may be substituted with one or two groups independently selected from $-(CH_2)_pR_1$, $-O(CH_2)_pR_1$, $-(CF_2)_pCO_2H$, C_1-C_7 alkyl, C_1-C_7 trifluoroalkyl, halo, $-(CH_2)_pOH$, cyano, phenylsulfonyl, phenyl, thiophenyl, thiocarboxy, C_1-C_7 trifluoroalkoxy, C_1-C_7 alkoxy, $-S(C_1-C_4 \text{ alkyl})$, $-SO(C_1-C_9 \text{ alkyl})$, $-SO_2(C_1-C_9 \text{ alkyl})$, $-SO_2NR_{14}R_{15}$, $(CH_2)_pCONR_{14}R_{15}$, $-(CH_2)_pNR_{16}SO_2(C_1-C_4 \text{ alkyl or trifluoroalkyl})$, or a heteroaryl selected from imidazolyl, triazolyl, tetrazolyl, thiazolyl, isoxazolyl, or oxazolyl, said heteroaryl being optionally substituted with $-(CH_2)_pR_1$; R_{14} and R_{15} are independently H, C_1-C_4 alkyl, $(CH_2)_pCO_2H$ or taken together with nitrogen to which they are bonded constitute a heterocyclic ring selected from the groups consisting of pyrrolidino or piperidino, said heterocyclic ring being optionally substituted with $-COOH$; R_{16} is H or C_1-C_4 alkyl.

The term " C_1-C_4 alkyl substituted phenyl" represents a phenyl substituted in any position with a C_1-C_4 alkyl as previously defined.

The term "ester group" is understood in the art. Preferably, an ester group is a C_1-C_4 alkyl especially methyl or ethyl.

The term "carboxy protecting group" as used in the specification refers to one of the ester derivatives of the carboxylic acid group commonly employed to block or protect the carboxylic acid group while reactions are carried out on other functional groups on the compound. The species of carboxy-protecting group employed is not critical so long as the derivatized carboxylic acid is stable to the condition of subsequent reaction(s) and can be removed at the appropriate point without disrupting the remainder of the molecule. See E. Haslam, Protective Groups in Organic Chemistry, J.G.W. McOmie, Ed., Plenum Press, New York, N.Y., 1973, Chapter

5, and T.W. Greene, Protective Groups in Organic Synthesis, John Wiley and Sons, New York, N.Y., 1981, Chapter 5. A related term is "protected carboxy," which refers to a carboxy-protecting groups.

The term "amino protecting group" as used in the specification refers to substituents of the amino group commonly employed to block or protect the amino functionality while reacting other functional groups on the compound. The species of amino-protecting group employed is not critical so long as the derivatized amino group is stable to the condition of subsequent reaction(s) and can be removed at the appropriate point without disrupting the remainder of the molecule. Preferred amino-protecting groups are t-butoxycarbonyl and the benzyloxycarbonyl. See J. W. Barton, Protective Groups in Organic Chemistry, J.G.W. McOmie, Ed., Plenum Press, New York, N.Y., 1973, Chapter 2, and T. W. Greene, Protective Groups in Organic Synthesis, John Wiley and Sons, New York, N.Y., 1981, Chapter 7. The related term "protected amino" defines an amino group substituted with an amino protecting group as previously discussed.

By virtue of their acidic moieties, the compounds of Formula I include the pharmaceutically acceptable base addition salts thereof. Such salts include those derived from inorganic bases such as ammonium and alkali and alkaline earth metal hydroxides, carbonates, bicarbonates, and the like, as well as salts derived from basic organic amines such as aliphatic and aromatic amines, aliphatic diamines, hydroxy alkamines, and the like. Such bases useful in preparing the salts of this invention thus include ammonium hydroxide, potassium carbonate, sodium bicarbonate, calcium hydroxide, methylamine, diethylamine, ethylenediamine, cyclohexylamine ethanolamine and the like. The potassium and sodium salt forms are particularly preferred.

Because of the heterocycle moiety, the compounds of Formula I can also exist as pharmaceutically acceptable acid addition salts. Acids commonly employed to form such salts include inorganic acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric and phosphoric acid, as well as organic acids such as para toluenesulfonic, methanesulfonic, oxalic, para bromophenylsulfonic, carbonic, succinic, citric, benzoic and acetic acid, and related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propionate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, 2-butyne-1,4 dioate, 3-hexyne-2, 5-dioate, benzoate, chlorobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, hippurate, β -hydroxybutyrate, glycollate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like salts.

The pharmaceutically acceptable salts of compounds of Formula I can also exist as various solvates, such as with water, methanol, ethanol, dimethylformamide, ethyl acetate and the like. Mixtures of such solvates can also be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent.

It is recognized that various stereoisomeric forms of the compounds of Formula I exist, for example the chiral carbon atom which is attached to the imidazole, R_4 , and R_5 . This invention is not limited to any particular stereoisomer but includes all possible individual isomers and mixtures thereof.

The synthesis and use of 1,3 imidazoles as angiotensin II antagonists is described in U.S. patent No. 5,073,566. U.S. patent 5,073,566 is herein incorporated by reference.

The tetrazolyl moieties of R_1 in Formula I (It is preferred that R_1 be protected as a nitrile during the coupling reactions) can be prepared by treating the cyano intermediates with an alkali metal azide such as sodium azide, ammonium chloride or triethylamine hydrochloride, and (optionally) lithium chloride in a nonreactive high boiling solvent such as N,N-dimethylformamide (DMF), preferably at a temperature from about 60-125°C. Preferably, tri-(n-butyl)tin azide or tetramethylguanadinium azide, neat or in a solvent such as tetrahydrofuran, dimethoxyethane, diethoxyethane, or the like, may be used in place of the alkali metal azide, ammonium chloride, lithium chloride, and DMF.

The carboxylic acids of Formula I can be prepared by the hydrolysis of the cyano intermediate (R_1 is protected as nitrile a during the coupling reactions). The hydrolysis involves the heating of the cyano derivative in an aqueous alcohol in the presence of a base such as sodium or potassium hydroxide. The salts of the carboxylic acid and the tetrazole final product are made by reacting the free acid or tetrazole with the appropriate base by standard procedures.

The compounds of Formula I which contain a sulfonamide in the R_1 moiety can be prepared by converting the carboxylic acid of R_1 to an acid chloride and then reacting the acid chloride with an alkyl sulfonamide by conventional techniques.

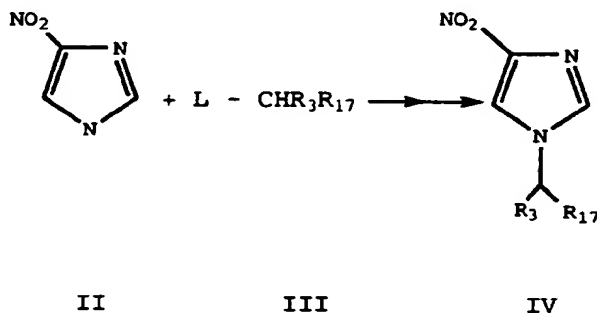
The compounds of Formula I which contain an alkoxy moiety (R_2 is an alkoxy) may be readily converted to hydroxy compounds of Formula I. For example, the alkoxy may be cleaved with boron tribromide to form the hydroxy moiety.

The desired products from the disclosed reactions can be isolated by conventional means, and preferably

by chromatography. Column chromatography is a preferred method. High pressure column chromatography over silica gel and high pressure reverse phase chromatography offer the most efficient way of purifying the final products. Alternatively, crystallization of the acid, tetrazole, or salts may be employed to purify the desired final product.

One process for preparing the compounds of Formula I involves the alkylation of an imidazole with an alkylating reagent III as summarized in Scheme 1.

Scheme 1



R₃ is the same as previously defined. R₁₇ is a protected carboxy, such as an ester; or when R₄ is (a), R₁₇ is a protected imidazolyl. See Greene, T.W., Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1981. To prepare the amides of Formula I, R₁₇ is a protected carboxy.

L is a good leaving group such as chloro, bromo, iodo, mesyl, tosyl, and the like. L may also be a hydroxy or a precursor which may be readily converted to a good leaving group by techniques known in the art.

This reaction usually involves approximately equimolar amounts of the two reagents, although other ratios, especially those wherein the alkylating reagent is in excess, are operative. The reaction is best carried out in a polar aprotic solvent wherein the compound is an alkali metal salt or other such alkylation conditions as are appreciated in the art. When the leaving group is bromo or chloro, a catalytic amount of iodide salt, such as potassium iodide may be added to speed the reaction. Preferred reaction conditions include the following: lithium bromide and dimethylformamide, potassium fluoride on alumina in THF, sodium bicarbonate in dimethylformamide, sodium hydride in dimethylformamide, potassium carbonate, potassium iodide, and either methylethyl ketone or acetone. The temperature of the reaction is preferably from about ambient temperature to about the reflux temperature of the reaction mixture. When elevated temperatures are employed, the reaction is generally complete in 1-4 hours.

When preparing the amides of Formula I, the protected carboxy, R₁₇, is readily converted to the carboxylic acid and then to the acid halide by techniques known in the art. See Greene, T.W., Protective Groups in Organic Synthesis, p. 152. Conversion of the acid to the corresponding acid chloride, for example, can be accomplished upon treatment with a reagent such as thionyl chloride or oxalyl chloride optionally in the presence of an aprotic nonreactive solvent. Preferred combinations include thionyl chloride treatment followed by reaction of the amine in potassium carbonate in tetrahydrofuran, or reaction of oxalyl chloride with the carboxylic acid.

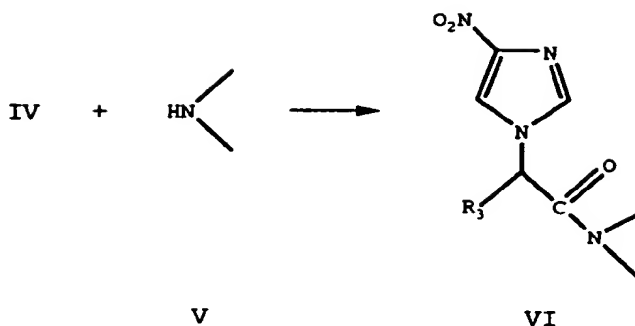
The acid halide of Compound IV may then be reacted with the desired amine to form the amides (R₄ is an amide) of the present invention. This reaction is summarized in Scheme 2.

Scheme 2

5

10

15



20

R_3 is the same as previously defined. When the amine (Compound V) contains a carbonyl group, it is preferred that carbonyl is protected during the reaction.

The amine employed in this scheme is dependent upon the desired amide of Formula I. For example, to produce a substituted proline derivative, the acid chloride of compound IV may be reacted with a substituted proline methyl ester (V). Likewise, to produce trifluoropropyl amide, the acid halide is reacted with trifluoropropylamine.

25

The coupling reaction between the acid halide of Compound IV and the amine may be accomplished by any of several known methods. The preferred method in this scheme is to react the acid halide, preferably the acid chloride, with the amine directly in THF or methylene chloride in the presence of triethylamine.

The resulting amide may be converted to the compounds of Formula I by techniques known in the art. See Duncia et al. *J. Org. Chem.* 56: 2395-2400 (1991).

30

Alternatively, Compound III may be converted to the acid chloride and reacted according to Schemes 2 to form the amide. This intermediate may then be alkylated according to the conditions described in Scheme 1 to form the nitro imidazole.

The compounds of this invention that contain a carboxamide-type linkage can be prepared according to Scheme 3.

35

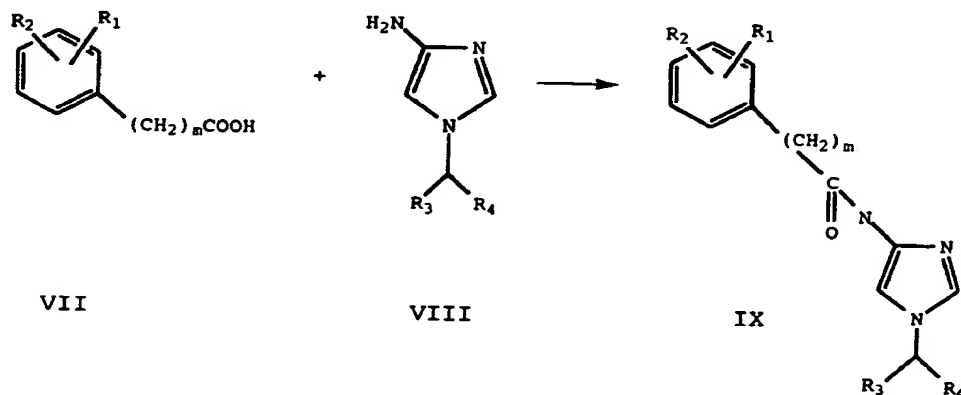
Scheme 3

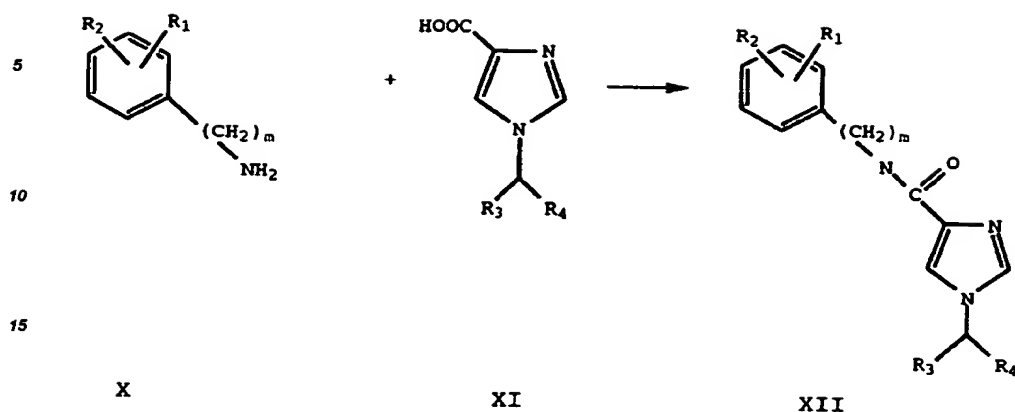
40

45

50

55





20 where R₁, R₂, R₃, R₄, and m are the same as previously defined.

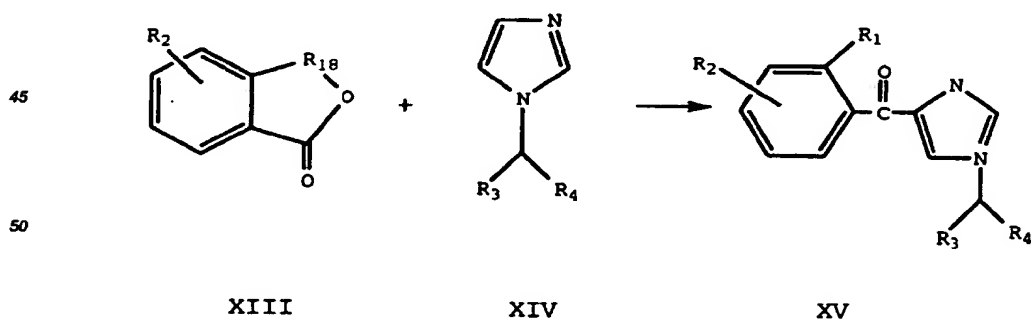
The transformation as depicted in Scheme 3 above can be accomplished by any of several known methods of coupling carboxylic acids to amines. For example, carboxylic acid VII or XI can be transformed into a corresponding acid halide, particularly an acid chloride, and then reacted with the appropriate amine to provide amides IX or XII as previously discussed.

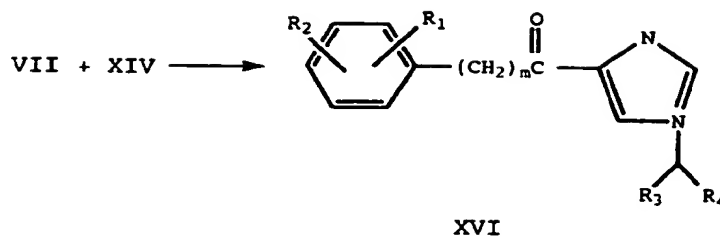
Alternatively, other amide condensing reagents may also be employed, such as 1,1'-carbonyldiimidazole or 1,3-dicyclohexylcarbodiimide. These reagents are usually employed in a nonreactive high boiling solvent such as dimethylformamide and optionally in the presence of reagents such as diisopropylethylamine, hydroxybenzotriazole, and the like in order to facilitate reaction.

30 If R₄ contains a carboxy moiety, the reaction is best carried out when the carboxy group is protected as an ester. When the coupling is complete the ester may be readily converted into the acid by methods known in the art. For example, the ester moiety may be hydrolyzed with an aqueous base such as 2N NaOH in methanol. The pH lowered to 3.0 with 5N HCL. The acid product may then be extracted by conventional means.

35 Ketone-containing compounds of Formula I can be prepared by reacting either an anhydride (Compound XIII) or the acid chloride of compound VII with Compound XIV to provide the corresponding ketones XV and XVI, respectively as described in Scheme 4.

Scheme 4





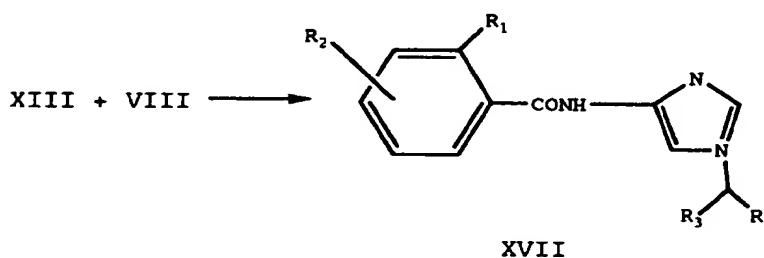
In Scheme 4 above, R_2 , R_3 , R_4 and m , are the same as previously defined. R_{1a} is SO_2 or CO . R_1 is SO_3H or CO_2H .

The reactions portrayed in Scheme 4 are generally known as Friedel-Crafts reactions. The reactions involves reacting approximately equimolar amounts of the acid chloride of compound VII or the anhydride (XIII) with reagent XIV in the presence of a Lewis acid, such as aluminum chloride, in a nonreactive polar solvent such as dimethylformamide or methylene chloride.

In a manner analogous to Scheme 4 above, the ketone containing compounds of Formula I (X is $-CO(CH_2)_m-$) may be prepared by converting a carboxylimidazole to an acid chloride and reacting the acid chloride with a substituted aromatic.

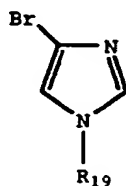
The preferred amide containing compounds of Formula I can be prepared according to the following Scheme 5:

Scheme 5



In Scheme 5, the amine is then reacted with the appropriate anhydride (XIII) by mixing the two reagents in one or more nonreactive solvents, such as dimethylformamide. This reaction gives products similar to those found in Scheme 3 above which are, in part, the preferred compounds of Formula I. Alternatively, the anhydride (XIII) can be reacted with one equivalent of an alcohol to provide a monoacid monoester (Compound VII) which may be reacted in accordance with Scheme 3.

The compounds of this invention which contain an amine linkage (X is $-NH-$) can be prepared by techniques known in the art. For example the Ullman reaction may be employed by reacting with a compound of the formula

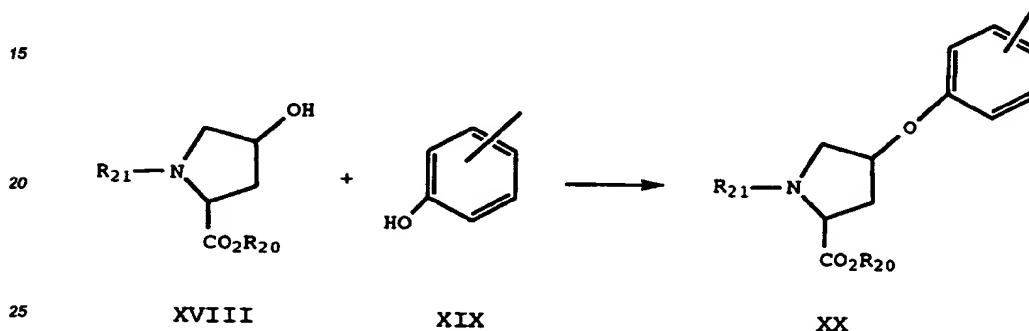


wherein R_{19} is a imidazole protecting group such as a benzyl functionality. The reaction is carried out in the presence of copper bronze or copper chloride in pyridine or dimethylformamide. The resulting product can be deprotected and alkylated in a manner analogous to Scheme 1.

The compounds of this invention that contain a ether linkage (X is -O-) may also be prepared by an Ullman reaction. This reaction is analogous to the preparation of the amine linkage except for beginning with the hydroxy analog of compound X.

The substituted phenoxy proline derivatives may be readily prepared in accordance with Scheme 6.

Scheme 6



In Scheme 6 above R_{21} is a amino protecting group, preferably carbobenzyloxy; R_{20} is a carboxy protecting group, preferably a C_1 - C_4 alkyl to form an ester. The phenol Compound XIX, is reacted in accordance with this Scheme to prepare the compounds of Formula I wherein R_{10} is a substituted phenyl as previously defined.

The reaction portrayed is known in the art as a Mitsunobu reaction. See Mitsunobu, O., *Synthesis* 1 (1981). Preferably, the reaction is carried out in the presence of triphenylphosphine and diethylazodicarboxylate in an aprotic solvent such as THF. At the completion of this scheme compound XX may be deprotected to form the amine and further reacted in accordance with Scheme 2.

As noted above, the compounds of this invention contain at least one chiral center, that being the carbon atom attached to the imidazole, R_3 and R_4 substituents. While all of the above schemes address reactions involving racemic reagents and products, each of the reactions can be performed using a chiral starting material to provide a particular enantiomer of interest. Alternatively, particular isomers can be isolated from the racemate by standard methods such as fractional crystallization, high pressure liquid chromatography, reverse phase chromatography and the like. These resolutions can be accomplished either on the final product Formula I, an intermediate, at any stage along the synthetic pathway, or on derivatives of the final product and intermediate. Preferably, Compound IV is separated into its enantiomers before the coupling of Scheme 2. Compound IV is separated by optical resolution employing (-)-cinchonidine as the resolving agent.

Clearly the coupling of the substituted benzoic acid or the substituted anhydride to the imidazolyl, Schemes 3 or 4, may occur at any time in the synthesis. Preferably, the coupling of Scheme 2 occurs prior to Scheme 3 or 4. However, one skilled in the art would appreciate that the order of the reactions is not critical as long as appropriate amino and carboxy protecting groups are employed.

In all of the above schemes, it is preferred that the reactions be carried out wherein all of the R_i groups are protected during the coupling reaction and subsequently deprotected. For example, if R_1 is to be a tetrazole, the reaction are best carried out with the cyano intermediate. However, one skilled in the art recognizes that many of these reactions can be performed on the free acid or tetrazole if the appropriate reaction conditions, blocking reagents, or the like are used. Since the R_i moieties are considerably different in their sensitivity to hydrolysis, the sequence for transforming intermediates of the Formula II to final products having both an acid and tetrazole group is not critical.

Compounds II, III, V, VII, VIII, X, XI, XIII, XIV, XVIII, XXIV, and any other reagents required for their transformation, are either commercially available, known in the art, or can be prepared by methods known in the art.

The following examples and preparations are provided merely to further illustrate the invention. The scope of the invention is not construed as merely consisting of the following examples.

In the following examples and preparations, melting point, nuclear magnetic resonance spectra, mass spectra, high pressure liquid chromatography over silica gel, N,N-dimethylformamide, palladium on charcoal, diisobutylaluminum hydride, and tetrahydrofuran are abbreviated M.Pt, NMR, MS, HPLC, DMF, Pd/C, DIBAL and THF, respectively. The terms "NMR" and "MS" indicate that the spectrum was consistent with the desired structure.

Preparation 1

2-Carboxy-6-hydroxybenzenesulfonic acid

Methyl 2-hydroxy-3-methoxybenzoate (0.027 moles, 5.0 g) was added to a suspension of sodium hydride (0.03 moles, 1.45 g of 50% in mineral oil) in 50 ml DMF and stirred at room temperature for 1 hour. Dimethylthiocarbamoyl chloride (0.03 moles, 3.73 g) in 40 ml DMF was added dropwise over 1 hour. The reaction was stirred for 18 hours. Ethyl acetate was added. The solution was thoroughly washed with brine, dried and condensed. The residue was purified by HPLC over silica gel eluted with 50% ethyl acetate in hexane to yield 0.9 g of O-(2-carbomethoxy-6-methoxyphenyl)-N,N-dimethylthiocarbamate. MS.

Calculated for $C_{12}H_{15}NO_4S$:

C, 53.52; H, 5.61; N, 5.20.

Found:

C, 53.35; H, 5.54; N, 5.07.

O-(2-Carbomethoxy-6-methoxyphenyl)-N,N-dimethylthiocarbamate (720 mg) was heated at 220° C for 100 minutes, and cooled to yield 700 mg of S-(2-carbomethoxy-6-methoxyphenyl)-N,N-dimethylthiocarbamate. MS.

Calculated for $C_{12}H_{15}NO_4S$:

C, 53.52; H, 5.61; N, 5.20.

Found :

C, 53.74; H, 5.60; N, 4.92.

S-(2-carbomethoxy-6-methoxyphenyl)-N,N-dimethylthiocarbamate (14.4 mmoles, 3.9 g) was dissolved in 66 ml formic acid. Hydrogen peroxide (24 ml of 30%) was added dropwise with cooling when required. The reaction was stirred at room temperature for 16 hours and condensed. Toluene (100 ml) was added to the residue. The toluene solution was concentrated. The solid was slurried in ether and filtered to yield 3.0 g of 2-Carbomethoxy-6-methoxybenzenesulfonic acid dimethylamine salt.

2-Carbomethoxy-6-methoxybenzenesulfonic acid dimethylamine salt (9.0 mmoles, 2.6 g) was added dropwise at -20° C to a solution of boron tribromide (27 mmoles, 3.8 ml) in 50 ml methylene chloride and stirred at -20° C for 10 minutes and at room temperature overnight. The reaction was quenched with water. The pH was adjusted to 8.0 using 2N NaOH. The aqueous solution was washed with methylene chloride. The pH of the water layer was adjusted to 1.0 with 2N HCL. The intermediate was extracted with ethyl acetate and condensed. The solid triturated with ethyl acetate and filtered to yield 1.6 g of 2-carboxy-6-hydroxybenzenesulfonic acid.

Preparation 2

N-Carbobenzyloxy-4-trans-hydroxy-L-proline methyl ester.

A solution of silver oxide (I) (1.08 moles, 250 g) in 1500 ml acetone was cooled to 5° - 0° C. N-carbobenzyloxy-4-trans-hydroxy-L-proline (0.5 moles, 132.6 g) was added. The solution was stirred for 25 minutes. Methyl iodide (1.2 moles, 170.4 g) was added at 6° C over 25 minutes. The reaction was stirred at room temperature for 5 hours, filtered, and concentrated. The intermediate was dissolved in ethyl acetate, filtered through silica gel and concentrated. MS.

Calculated for $C_{14}H_{17}NO_6$:

C, 60.21; H, 6.13; N, 5.01.

Found:

C, 60.40; H, 6.26; N, 5.06.

Preparation 3N-Carbobenzyloxy-4-cis-phenoxy-L-proline methyl ester.

5 N-Carbobenzyloxy-4-trans-hydroxy-L-proline methyl ester (0.267 moles, 74.5 g), phenol (0.282 moles, 26.5 g), and triphenylphosphine (0.279 moles, 73.3 g) were dissolved in 750 ml of THF, and cooled to -3° C. Diethyl azidodicarboxylate (0.284 moles, 45 ml) was added dropwise over 2 hours. The reaction was stirred at room temperature overnight and then concentrated. The residue was dissolved in ether, filtered and concentrated. The intermediate was chromatographed over silica gel eluted with a gradient of 0-40% ethyl acetate in hexane to yield 41.0 g. (NMR)

Preparation 44-Bromo-t-butoxybenzene.

15 4-Bromophenol (57.8 mmol, 10.0 g) was added to a -30° C solution of isobutylene (40 ml) and methylene chloride (50 ml) and then cooled to -78° C. Trifluoromethanesulfonic acid (4 mmol, 0.35 ml) was added. The mixture was held at -78° C for 4 hours and then allowed to warm to room temperature. Triethylamine (0.5 ml) was added; the solvent was removed. The residue was chromatographed over silica gel eluted with 1% ethyl acetate in hexane to yield 12.4 g. MS.

Calculated for $C_{10}H_{13}BrO$:

C, 52.42; H, 5.72.

Found:

25 C, 52.69; H, 5.67.

Preparation 54-t-Butoxyphenol.

30 Sec-butyllithium (53.2 mmol, 41 ml of 1.3M in hexane) was added dropwise at -78° C to 4-bromo-t-butoxybenzene (53.2 mmol, 12.2 g) in 200 ml THF, stirred at -78° C for 1 hour, and added slowly to a solution of triisopropylborate (58.5 mmol, 11.0g) in 50 ml THF while maintaining the temperature below -60° C. The mixture was allowed to warm gradually to -20° C. Chilled acetic acid (80 mmol, 9.6 ml) was added. Hydrogen peroxide (58.5 mmol, 5.9 ml of 30% diluted with 5 ml water) was added dropwise over 15 minutes while maintaining the temperature below 0° C. After stirring 10 minutes, the solution was washed with ammonium sulfate solution, dried, and concentrated. The residue was triturated with hexane and filtered to yield 4.2 g of 4-t-butoxyphenol. MS.

Calculated for $C_{10}H_{14}O_2$:

40 C, 72.26; H, 8.49.

Found:

C, 72.54; H, 8.27.

Preparation 6Diethyl-(4-hydroxy)-phenethylphosphonate.

45 A solution of tetraethylmethylenediphosphonate (6.22 g, 21.6 mmol) in 30 mL of anhydrous THF at -30° C under N_2 was treated with nBuLi (15.0 mL, 1.6 M solution in hexanes) dropwise via syringe. The resulting solution was warmed to 0° C for 30 min., and then cooled back to -30° C. 4-Benzyloxybenzaldehyde was then introduced via canula as a solution in 15 mL of anhydrous THF. After warming to room temperature and stirring for 2 hours, the reaction was quenched by pouring into H_2O (200 mL). The aqueous was extracted with ethyl acetate (3x100 mL). The organic was dried (Na_2SO_4) and concentrated *in vacuo* to give an oil. The crude product was chromatographed (SiO_2 , 25% hexane/ethyl acetate) to give 6.1 g (82%) of the unsaturated phosphonate as a light yellow oil that solidified on standing.

Calculated for $C_{19}H_{23}O_4P$:

C, 65.89; H, 6.69.

Found:

C, 66.15; H, 6.59.

The phosphonate from the previous reaction (6.1 g, 17.5 mmol) was dissolved in 100 mL of absolute ethanol, and treated with 1.15 g of 5% Pd/C. The mixture was hydrogenated at 40 psi for 1 hour, and then passed through a pad of celite. The filtrate was concentrated in vacuo to yield 4.5 g (100%) of diethyl-(4-hydroxy)-phenethylphosphonate as a light yellow oil.

Preparation 7

Diethyl-(4-hydroxy)-phenylphosphate.

4-Benzyloxyphenol (15.0 g, 75 mmol) was dissolved in 100 mL of anhydrous THF and cooled to 0°C. NaH (3.0 g, 75 mmol, 60% dispersion in mineral oil) was then introduced in small portions. When gas evolution ceased, diethylchlorophosphate was introduced dropwise via syringe. After stirring the reaction for 1 hour, the mixture was poured into H₂O/ethyl acetate (150 mL ea.). The layers were separated, and the organic washed with 0.1 N NaOH (2x100 mL). The organic was dried (Na₂SO₄) and concentrated in vacuo to a light yellow liquid. Chromatography SiO₂, first 20% ethyl acetate/hexanes followed by 40% hexanes/ethyl acetate) provided 23.4 g (93%) of diethyl-(4-benzyloxy)-phenyl phosphate as a colorless liquid.

Diethyl-(4-benzyloxy)-phenyl phosphate (15.0 g, 44.7 mmol) was dissolved in 150 mL of 30% ethyl acetate in ethanol, along with 0.5 mL of concentrated HCl. To this solution was added 3.0 g of 10% Pd/C. The mixture was hydrogenated at 1 atm for 18 hours and then passed through a pad of celite to remove the catalyst. The filtrate was concentrated in vacuo, and the residue chromatographed (SiO₂, ethyl acetate) to provide 10.4 g (94%) of diethyl-4-hydroxy-phenyl phosphate as an amber liquid.

Preparation 8

Diethyl-(4-hydroxy)-benzenephosphonate

To a solution of 4-benzyloxybromobenzene (10.0 g, 38 mmol) in 150 mL of anhydrous THF at -78°C under N₂ was added nBuLi (26.1 mL, 41.8 mmol, 1.6 M in hexanes) dropwise over 30 minutes. After stirring for 15 minutes, diethylchlorophosphate (6.0 mL, 41.8 mmol) was added dropwise via syringe. The resulting mixture was allowed to gradually warm to room temperature whereupon the reaction was quenched by pouring into H₂O/ethyl acetate (200 mL ea.). The layers were separated, and the aqueous was extracted with ethyl acetate (2x100 mL). The organic was dried (Na₂SO₄), and concentrated in vacuo to a yellow liquid. Chromatography (SiO₂, 50-100% ethyl acetate/hexanes) provided 11.1 g (91%) of diethyl-(4-benzyloxy)-benzenephosphonate as a colorless liquid. MS.

Diethyl-(4-benzyloxy)-benzenephosphonate (11.0 g, 34 mmol) was hydrogenated as described in the previous example. Chromatography of the crude reduction product provided 4.3 g (52%) of diethyl-(4-hydroxy)-benzenephosphonate as a light yellow liquid. MS.

Preparation 9

4-(pyrrolidinosulfonyl)-phenol

To a solution of pyrrolidine (17 mL, 237 mmol) in 20 mL of H₂O at room temperature was added p-flourobenzenesulfonyl chloride (15 g, 79 mmol) in portions over a 5 minute period. After 1 hour, the solution was diluted with 100 mL of H₂O and extracted with ethyl acetate (3x50 mL). The organic was dried (Na₂SO₄) and concentrated in vacuo to give 12.3 g (72%) of 4-(pyrrolidinosulfonyl)-flourobenzene as a colorless oil that solidified on standing. This material was used in the following reaction without further purification. MS.

To a solution of benzyl alcohol (6.63 mL, 62.0 mmol) in 200 mL of anhydrous DMF at room temperature was added NaH (2.40 g, 60.0 mmol, 60% dispersion in mineral oil) in small portions. After stirring for 30 minutes, 4-(pyrrolidinosulfonyl)-flourobenzene (11.0 g, 51.2 mmol) was added over a 10 minute period. After 30 minutes, a white precipitate formed. The reaction was then diluted with 100 mL of H₂O, and the product isolated by vacuum filtration. The solid was dried in vacuo to give 14.85 g (95%) of the 4-(pyrrolidinosulfonyl)-phenylbenzylether as a white solid. MS.

A solution of 4-(pyrrolidinosulfonyl)-phenylbenzylether (10.0 g, 33.1 mmol) was dissolved in 100 mL of absolute ethanol. This solution was treated with 2.5 g of 10% Pd/C. The mixture was hydrogenated at 40 psi for 2 hours. The catalyst was then removed by passing the reaction mixture through a pad of celite. The filtrate was concentrated in vacuo to provide 6.8 g (90%) of 4-(pyrrolidinosulfonyl)-phenol as a white solid. MS. 4-(methyaminosulfonyl)-phenol was prepared in a similar manner.

Preparation 10N-(4-hydroxybenzamido)-L-proline methyl ester.

5

L-Proline methyl ester hydrochloride (7.2 g, 43.8 mmol) was dissolved in 100 mL of anhydrous DMF at 0°C. To this solution was added triethylamine (4.2 g, 43.8 mmol). After vigorous stirring for 1 hour, the solid triethylamine hydrochloride was removed by filtration. To the filtrate was added 4-benzyloxybenzoic acid (10.0 g, 43.8 mmol) followed by DCC (9.9 g, 48.2 mmol). The reaction mixture was allowed to stir overnight at room temperature. The solid DCU was then removed by filtration, and the filtrate distributed between H₂O/ethyl acetate (300 mL ea.). The organic was washed several times with 200 mL portions of H₂O to remove DMF. The organic was dried (Na₂SO₄), and concentrated in vacuo to a solid residue that was chromatographed (SiO₂, 15-100% ethyl acetate/hexanes). Isolation provided 5.3 g (35%) of N-(4-benzyloxybenzamido)-L-proline methyl ester as a white solid. MS.

The above amide (10.0 g, 29.4 mmol) dissolved in 75 mL of absolute ethanol. To this solution was added 3 g of 10% Pd/C. The mixture was hydrogenated at 1 atm for 5 hours. The catalyst was then removed by passing the reaction through a pad of celite. Concentration of the filtrate provided crude N-(4-hydroxybenzamido)-L-proline methyl ester that was purified by chromatography (SiO₂, 30% ethyl acetate/hexanes) to provide 6.3 g (86%) as a white solid. MS.

20

Preparation 11(R)-α-hexyl-4-nitro-1H-imidazole-1-acetic acid (-)-cinchonidine salt

To a suspension of 5.89 g (0.02 mol) of (-)-cinchonidine in 80 mL water was added 2.78 mL (2.02 g, 0.02 mol) triethylamine. The mixture was warmed to about 40-45°C. A solution of 10.21 g (0.04 mol) of a racemic mixture of α-hexyl-4-nitro-1H-imidazole-1-acetic acid in 40 mL technical grade ethanol was added to the warm suspension with stirring. (The pH of the mixture was adjusted to 6.9-7.4 by addition of triethylamine or aqueous hydrochloric acid as required.) The resulting suspension was then heated to about 85°C. The resulting solution was allowed to cool gradually to ambient temperature with slow stirring. The precipitated salt was filtered, washed with about 30 mL of ethanol-H₂O (1:2), and dried at 50°C in vacuo to constant weight. The reaction produced 9 g of (R)-α-hexyl-4-nitro-1H-imidazole-1-acetic acid (-)-cinchonidine salt. A portion of the product was converted to the free acid and then derivatized as the methyl ester (diazomethane) and analyzed by HPLC on a chiral column. The analysis indicated that the acid derived from the product had an ee of 94%. Recrystallization of the product salt from ethanol - water 1:1 (1:1 volumes) provided 7.4 g of the pure salt, ee > 99% (HPLC), M.Pt. 205° C (dec). (NMR).

Calculated for C₃₀H₃₉N₅O₆:
C: 65.55; H: 7.15; N: 12.74.

Found:
C: 65.32; H: 7.25; N: 12.74.

Preparation 12(R)-α-hexyl-4-nitro-1H-imidazole-1-acetic acid

45

A 2.80 g portion of the pure cinchonidine salt obtained as described in Example 1 was mixed with 20 mL of 1M HCL. The resulting suspension was extracted with 30 mL of ethyl acetate. The ethyl acetate phase was dried (MgSO₄) and concentrated to dryness, providing 0.82 g (63%) of (R)-α-hexyl-4-nitro-1H-imidazole-1-acetic acid. M.Pt. 112-114°C.

50

Example 1N-Ethyl-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octanoamide.

4-Nitroimidazole (0.29 moles, 32.9 g in 30 ml DMF) was treated portionwise with sodium hydride (0.29 moles, 11.6 g, 60% in mineral oil) and stirred for 45 minutes. Ethyl 2-bromooctanoate (0.29 moles, 73.1 g) was added dropwise over 1 hour. The reaction was stirred overnight at room temperature, poured onto ice water, and extracted with ethyl acetate. The organic phase was washed with brine, dried and concentrated to yield 91 g of ethyl 2-(4-nitro-1H-imidazol-1-yl)octanoate. MS.

Ethyl 2-(4-nitro-1H-imidazol-1-yl)octanoate (17 mmol, 5.0 g) and ethylamine (20 ml) were stirred in 150 ml ethanol at room temperature for 16 hours. The reaction was added to ice water, extracted with ethyl acetate, washed with water, dried over sodium sulfate and concentrated. The oil crystallized upon standing to yield 3.9 g of N-Ethyl-2-(4-nitro-1H-imidazol-1-yl)octanoamide. MS.

Calculated for $C_{13}H_{22}N_4O_3 \cdot 1/4 H_2O$:

C, 54.40; H, 7.83; N, 19.52.

Found:

C, 54.45; H, 7.73; N, 19.12.

N-Ethyl-2-(4-nitro-1H-imidazol-1-yl)octanoamide (5.3 mmol, 1.5 g) was reduced by hydrogenation at 40 psi over Pd/C. The reaction was filtered and concentrated. The residue was dissolved in 10 ml THF and added to a solution of 2-sulfobenzoic acid cyclic anhydride (5.3 mmol, 0.98 g) in 10 ml THF. After stirring for 10 minutes at room temperature; the product precipitated and was collected by filtration, washed with ether and dried to yield 1.1 g of product. MS.

M.Pt.: Dec. 235° C.

Calculated for $C_{20}H_{28}N_4O_5S$:

C, 55.03; H, 6.46; N, 12.83.

Found

C, 54.75; H, 6.49; N, 13.08.

Example 2

N-Propyl-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl] octanoamide.

Ethyl 2-(4-nitro-1H-imidazole-1-yl)octanoate (17 mmol, 5.0 g) was reacted with propylamine as in Example 1 to yield 2.5 g of N-propyl-2-(4-nitro-1H-imidazol-1-yl)octanoamide. MS.

N-Propyl-2-(4-nitro-1H-imidazol-1-yl)octanoamide (2.3 mmol, 0.7 g) was reduced to the amine and reacted with 2-sulfobenzoic acid cyclic anhydride (2.3 mmol, 0.423 g) as in Example 1 to yield 0.70 g of product. MS.

M.Pt.: Dec. 235° C.

Calculated for $C_{21}H_{30}N_4O_5S \cdot 1.5 H_2O$:

C, 52.78; H, 6.91; N, 11.71.

Found:

C, 52.86; H, 6.37; N, 11.16.

Example 3

N-(2,2,2-Trifluoroethyl)-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octanoamide.

2-(4-Nitro-1H-imidazol-1-yl)octanoic acid (7.8 mmol, 2.0 g) was treated with 25 ml oxalyl chloride, concentrated and added to a solution of trifluoroethylamine hydrochloride (7.8 mmol, 1.06 g) and triethylamine (2 ml) in 50 ml THF. After stirring at room temperature for 16 hours, the mixture was added to ice, extracted with ethyl acetate, dried over sodium sulfate, and concentrated. The intermediate was chromatographed over silica gel to yield 0.6 g of N-(2,2,2-trifluoroethyl)-2-(4-nitro-1H-imidazol-1-yl)octanoamide. MS.

Calculated for $C_{11}H_{19}F_3N_4O_3$:

C, 46.43; H, 5.69; N, 16.66.

Found:

C, 46.56; H, 5.88; N, 16.37.

N-(2,2,2-Trifluoroethyl)-2-(4-nitro-1H-imidazol-1-yl)octanoamide (1.5 mmol, 0.5 g) was reduced and reacted with 2-sulfobenzoic acid cyclic anhydride (1.4 mmol, 0.27 g) as in Example 1 to yield 500 mg of product. MS.

M.Pt.: Dec. 257-259° C.

Calculated for $C_{20}H_{25}F_3N_4O_5S \cdot H_2O$:

C, 47.26; H, 5.35; N, 11.01.

Found:

C, 47.39; H, 5.01; N, 10.82.

Exempl 4N-[2-(1-Hydroxy-2-methyl)propyl]-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octanoamide.

2-(4-Nitro-1H-imidazol-1-yl)octanoic acid (3.9 mmoles, 1.0 g) was converted to the acid chloride and reacted with 2-amino-2-methyl-1-propanol (5.85 mmoles, 0.52 g) as in Example 3 to yield 0.465 g of N-[2-(1-hydroxy-2-methyl)propyl]-2-(4-nitro-1H-imidazol-1-yl)octanoamide.

N-[2-(1-Hydroxy-2-methyl)propyl]-2-(4-nitro-1H-imidazol-1-yl)octanoamide (0.52 mmoles, 170 mg) was reduced and reacted with 2-sulfobenzoic acid (0.52 mmoles, 96 mg) as in Example 1 to yield 53 mg of product. MS.

M.Pt.: 148-158°C.

Calculated for $C_{22}H_{32}N_4O_6S$:

C, 54.98; H, 6.71; N, 11.66.

Found:

C, 51.49; H, 5.53; N, 8.32.

Example 52-[1-[1-[(2-oxo-1-imidazolidinyl)carbonyl]heptyl]-1H-imidazol-4-yl]amino]carbonyl]benzenesulfonic acid.

Prepared as in Example 3. MS. Yield of product, 17%.

M.Pt.: 219-228°C.

Calculated for $C_{21}H_{27}N_5O_6S$:

C, 52.82; H, 5.70; N, 14.66.

Found:

C, 51.19; H, 5.54; N, 12.65.

Example 62-[1-[1-[(2-thioxo-1-imidazolidinyl)carbonyl]heptyl]-1H-imidazol-4-yl]amino]carbonyl]benzenesulfonic acid.

Prepared as in Example 3. Yield of product, 11%. MS.

M.Pt.: 203-211°C.

Calculated for $C_{21}H_{27}N_5O_5S$:

C, 51.10; H, 5.51; N, 14.19.

Found:

C, 49.30; H, 5.71; N, 13.69.

Example 7N-(2-Pyridyl)-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octanoamide.

Prepared as in Example 3. Yield of product, 23%. MS.

M.Pt.: 165-173 °C.

Calculated for $C_{23}H_{27}N_5O_6S$:

C, 56.89; H, 5.61; N, 14.42.

Found:

C, 52.50; H, 4.75; N, 9.72.

Example 8N-(2-Hydroxyphenyl)-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octanoamide.

Prepared as in Example 3. Yield of product, 33%. MS.

M.Pt.: 138-147°C.

Calculated for $C_{24}H_{28}N_4O_6S \cdot 1.25 \text{ HCl}$:

C, 52.78; H, 5.40; N, 10.26.

Found:

C, 52.75; H, 5.23; N, 9.93.

Example 9

N-(2-Carboxyphenyl)-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octanoamide.

N-(2-Carboethoxyphenyl)-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octanoamide. was prepared as in Example 3. The ester (100 mg) was hydrolyzed in 1 ml of 1N NaOH and 0.2 ml methanol for 1 hour at room temperature and acidified with 1N HCl. The solid was filtered and dried for a 88% yield. MS.

M.Pt.: 163-168°C.

Calculated for $C_{25}H_{28}N_4O_7S \cdot 1.25H_2O$:

C, 54.49; H, 5.57; N, 10.17.

Found:

C, 54.58; H, 5.18; N, 9.75.

Example 10

2-[4-(3-Hydroxy-2-sulfobenzoyl)amino-1H-imidazol-1-yl]octanoic acid.

2-Carboxy-6-hydroxybenzenesulfonic acid (1.8 mmole, 400 mg) was dissolved in 15 ml of oxalyl chloride. One drop of DMF was added. The reaction was stirred for 30 minutes at room temperature. The solvent was removed in vacuo, and 20 ml THF added. A solution of ethyl 2-(4-amino-1H-imidazol-1-yl)octanoate (prepared by the reduction of 1.8 mmoles of ethyl 2-(4-nitro-1H-imidazol-1-yl)octanoate in ethanol with 5% Pd/C) in 40 ml THF and 2.0 mmoles of triethylamine was added dropwise. The reaction was stirred at room temperature for 3 hours; ethyl acetate was added. The solution was washed with water, dried over sodium sulfate and concentrated. The intermediate was slurried in ether, filtered, chromatographed over silica gel eluted with 15% methanol in methylene chloride. The ester was hydrolyzed in 20 ml methanol and 45 ml of 2N NaOH at room temperature for 2 hours. The solvent was removed; water was added. The pH was adjusted to 2.0 using 5 N HCL. The product was extracted into ethyl acetate, dried over sodium sulfate and concentrated to yield 2-[4-(3-Hydroxy-2-sulfobenzoyl)amino-1H-imidazol-1-yl]octanoic acid. MS.

M.Pt.: 238-240 °C.

Calculated for $C_{18}H_{23}N_3O_7S \cdot 1/2 H_2O$:

C, 49.71; H, 5.50; N, 9.60.

Found:

C, 49.73; H, 5.38; N, 9.30.

Example 11

1-[1-Oxo-1-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-D-proline.

A mixture of stereoisomers was prepared as in Example 21.

Isomer A: Yield 9% MS.

M.Pt.: 145-150°C.

Calculated for $C_{23}H_{30}N_4O_7S$:

C, 54.53; H, 5.97; N, 11.06.

Found:

C, 54.34; H, 6.06; N, 11.03.

Isomer B: Yield 5% MS.

M.Pt.: 148-155°C.

Calculated for $C_{23}H_{30}N_4O_7S$:

C, 54.53; H, 5.97; N, 11.06.

Found:

C, 54.52; H, 6.08; N, 10.93.

Example 12

1-[1-Oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-4-cis-phenoxy-L-proline.

N-Carbobenzyloxy-4-cis-phenoxy-L-proline methyl ester (0.115 moles, 41 g) was hydrogenated in ethanol over 5% Pd/C and concentrated.

2-Bromooctanoic acid (0.116 moles, 26 g) was added dropwise to a solution of oxalyl bromide (75 g) in 50 ml methylene chloride at ice bath temperature; 1 drop of DMF was added. The solution was stirred at room temperature for 1.5 hours and concentrated. The residue was dissolved in THF and added dropwise at ice bath temperature to a solution of the proline and triethylamine (45 ml) in THF. The reaction was stirred overnight at room temperature, filtered, and concentrated. The oil was dissolved in ethyl acetate, washed with brine, dried over sodium sulfate and concentrated. The product was chromatographed over silica gel eluted with 0-30% ethyl acetate in hexane to yield 26 g 1-(2-bromo-1-oxo)octyl-4-cis-phenoxy-L-proline methyl ester. (NMR)

4-Nitroimidazole (66.3 mmoles, 7.5 g) was dissolved in 200 ml DMF. Sodium hydride (75 mmoles, 3.0 g of 60% in mineral oil) was added portionwise. The solution was stirred for 1 hour. 1-(2-Bromo-1-oxo)octyl-4-cis-phenoxy-L-proline methyl ester (60 mmoles, 25.6 g) was added. The reaction was stirred at room temperature overnight. The reaction was concentrated; the residue was dissolved in ethyl acetate, washed twice with brine, dried over sodium sulfate and concentrated. The intermediate was chromatographed over silica gel eluted with 25-75% ethyl acetate in hexane.

Isomer A: yield 40% MS.

Calculated for $C_{23}H_{30}N_4O_6$:

C, 60.16; H, 6.67; N, 11.95

Found:

C, 60.25; H, 6.59; N, 12.21.

Isomer B: yield 16% MS.

Calculated for $C_{23}H_{30}N_4O_6$:

C, 60.25; H, 6.59; N, 12.22.

Found:

C, 60.43; H, 6.63; N, 12.26.

1-[1-oxo-2-(4-nitro-1H-imidazol-1-yl)octyl]-4-cisphenoxy-L-proline methyl ester, (isomer A, 22.7 mmoles, 10.4 g) was reduced in ethanol with 5% Pd/C and reacted with 2-sulfobenzoic acid cyclic anhydride (34.2 mmoles, 6.5 g) as in Example 1 to yield 9.2 g of ester. MS. The ester was hydrolyzed in 25 ml ethanol and 100 ml 1N sodium hydroxide at room temperature for 1 hour and concentrated. The residue was dissolved in a minimum volume of water. The pH was adjusted to 2.4 using 2 N HCL. The precipitate was filtered and dried to yield 6.0 g of product. MS.

M.Pt.: 180-190° C.

Calculated for $C_{29}H_{34}N_4O_8S$:

C, 58.18; H, 5.72; N, 9.36.

Found:

C, 58.18; H, 5.78; N, 9.50.

Isomer B was treated in a similar procedure to yield 90% yield of acid.

M.Pt.: >200° C.

Calculated for $C_{29}H_{34}N_4O_8S \cdot 1/2H_2O \cdot 1/2NaCl$:

C, 54.69; H, 5.54; N, 8.80.

Found:

C, 54.21; H, 5.46; N, 8.77.

Example 13

1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]heptyl]-4-cis-phenoxy-L-proline.

2-(4-nitro-1H-imidazol-1-yl)heptanoic acid (4 mmoles, 0.98 g, prepared as in Example 1) was stirred for 1 hour in 25 ml oxalyl chloride and concentrated. The residue was dissolved in methylene chloride (100 ml) and added dropwise to a solution of 4-cis-phenoxy-L-proline methyl ester (4 mmoles, 0.9 g) and triethylamine (0.56 ml) in 100 ml methylene chloride. The reaction was stirred for 2 hours at room temperature and then added to ice water. The organic layer was washed with water, dried over sodium sulfate, concentrated. The residue was chromatographed over silica gel eluted with a gradient of 50-75% ethyl acetate in hexane.

Isomer A intermediate: yield 41% MS.

Isomer B intermediate: yield 28%. MS.

Isomer A intermediate was further reacted as in Example 12 to yield the acid product. MS.

Calculated for $C_{28}H_{32}N_4O_8S$:

C, 57.52; H, 5.52; N, 9.58.

Found:

C, 56.87; H, 6.13; N, 10.33.

Example 14

1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]hexyl]-4-cis-phenoxy-L-proline

Prepared as in Example 12.

Isomer A: Yield 48%. MS.

M.Pt.: Dec. 215-220° C

Calculated for $C_{27}H_{30}N_4O_8S \cdot H_2O \cdot NaCl$:

C, 50.12; H, 4.98; N, 8.66.

Found:

C, 49.79; H, 4.81; N, 8.71.

Isomer B: Yield 29%. MS.

M.Pt.: Dec. 210° C

Calculated for $C_{27}H_{30}N_4O_8S \cdot H_2O$:

C, 55.09; H, 5.48; N, 9.52.

Found:

C, 55.39; H, 5.36; N, 9.15.

Example 15

1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]-8,8,8-trifluorooctyl]-4-cis-phenoxy-L-proline.

6-Bromohexanoic acid (0.51 moles, 100 g) was heated under SF_4 at 1300° C for 8 hours. Methylene chloride was added. The solution was filtered and concentrated. The resulting black oil, 6-Bromo-1,1,1-trifluorohexane, was distilled.

B Pt. 158-164° C/760 mm.

6-Bromo-1,1,1-trifluorohexane (0.228 moles, 50 g) was added to a solution of sodium iodide (51 g) in 250 ml acetone and stirred for 1 hour at room temperature. The solution was filtered and concentrated. The residue was slurried in ether, filtered and concentrated to yield 56 g, 92% of iodide. Ethyl acetoacetate (0.125 moles, 16.45 g) was added slowly to sodium hydride (0.126 moles, 5.06 g of 60% in mineral oil). The iodide (0.115 moles, 30.6 g) was added. The reaction was heated at 50° C for 16 hours and then poured into ice water. The intermediate was extracted with ethyl acetate, dried over sodium sulfate and concentrated. The residue was chromatographed over silica gel eluted with ethyl acetate in hexane to yield 13.3 g of ethyl 6,6,6-trifluorohexylacetoacetate. MS.

Ethyl 6,6,6-trifluorohexylacetoacetate was added at -35° C to a solution of sodium (50 mmoles, 1.15 g) in 150 ml ethanol and stirred for 15 minutes. N-Bromosuccinimide (50 mmoles, 8.9 g) was added. The solution was allowed to warm to room temperature and stirred for 2.5 hours. The mixture was poured into water. The intermediate was extracted with hexane. The solvent was removed. The oil was chromatographed over silica gel eluted with hexane to yield 13.6 g of ethyl 2-bromo-8,8,8-trifluorooctanoate. MS.

4-Nitroimidazole (43 mmoles, 4.86 g) was reacted with sodium hydride (43 mmoles, 1.72 g) and then ethyl 2-bromo-8,8,8-trifluorooctanoate (43 mmoles, 13.2 g) as in Example 1. The ester was hydrolyzed in 10 ml methanol and 30 ml 2N NaOH to yield a quantitative yield of 2-(4-nitro-1H-imidazol-1-yl)-8,8,8-trifluorooctanoic acid. (NMR)

The acid was further reacted as in Example 13 to produce the stereoisomers of 1-[1-oxo-2-(4-nitro-1H-imidazol-1-yl)-8,8,8-trifluorooctyl]-4-cis-phenoxy-L-proline methyl ester. (NMR) The isomers were separated as in Example 1; A isomer was further reacted as previously described. The product was chromatographed over silica gel eluted with 5% methanol in chloroform to produce 1-[1-oxo-2-[4-(2-Sulfobenzoyl)amino-1H-imidazol-1-yl]-8,8,8-trifluorooctyl]-4-cis-phenoxy-L-proline.

Isomer A: Yield 13%. MS.

Calculated for $C_{29}H_{30}F_3N_4O_8S \cdot 0.6HCl$:

C, 51.64; H, 4.72; N, 8.31.

Found:

C, 51.58; H, 4.80; N, 8.18.

5 Example 16

1-[1-Oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]-7,7,7-trifluoroheptyl]-4-cis-phenoxy-L-proline.

2-(4-Nitro-1H-imidazol-1-yl)-7,7,7-trifluoroheptanoic acid was prepared as in Example 15. (NMR). The acid
10 was further reacted as in Example 13 to produce 1-[1-Oxo-2-(4-nitro-1H-imidazol-1-yl)-7,7,7-trifluoroheptyl]-4-cisphenoxy-L-proline methyl ester. (NMR)

The ester was reacted as in Example 15 to produce 1-[1-Oxo-2-[4-(2-Sulfobenzoyl)amino-1H-imidazol-1-yl]-7,7,7-trifluoroheptyl]-4-cis-phenoxy-L-proline.

Isomer A: yield 21%, MS.

15 Calculated for $C_{28}O_{29}F_3N_4O_8S \cdot 0.9HCl$:

C, 50.09; H, 4.49; N, 8.44.

Found:

C, 50.13; H, 4.66; N, 8.44.

Isomer B: yield 26%, MS.

20 Calculated for $C_{28}O_{29}F_3N_4O_8S$:

C, 52.66 H, 4.58; N, 8.77.

Found:

C, 52.80; H, 4.85; N, 8.63.

25 Example 17

1-[1-Oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-4-cis-(3-pyridyloxy)-L-proline.

4-cis-(3-Pyridyloxy)-L-proline methyl ester (5.32 mmoles, 1.18 g (prepared as in Preparation 3 followed
30 by the deprotection of N-carbobenzyloxy-4-cis-(3-pyridyloxy)-L-proline methyl ester in ethanol with 5% Pd/C), 2-(4-nitro-1H-imidazol-1-yl)octanoic acid (5.32 mmoles, 1.36 g), and hydroxybenzotriazole (5.85 mmoles, 0.8 g) were dissolved in 5 ml DMF. After 5 minutes dicyclohexylcarbodiimide (5.85 mmoles, 1.21 g) was added. The reaction was stirred for 60 hours at room temperature. Ethyl acetate (15 ml) was added. The solution was filtered, washed with water, dried over sodium sulfate and concentrated. The residue was chromatographed
35 over silica gel eluted with 1% methanol in chloroform to produce 1-[1-Oxo-2-(4-nitro-1H-imidazol-1-yl)octyl]-4-cis-(3-pyridyloxy)-L-proline methyl ester.

Isomer A: 0.63 g; MS.

Isomer B: 0.37 g; MS.

Each isomer was reacted as in Example 1 to yield 1-[1-Oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-4-cis-(3-pyridyloxy)-L-proline.
40

Isomer A: Yield 3 %, MS.

Isomer B: Yield 3 %, MS.

Example 18

45

1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-4-cis-(4-methoxyphenoxy)-L-proline

N-Carbobenzyloxy-4-cis-(4-methoxyphenoxy)-L-proline methyl ester (prepared as in Preparation 3) was
50 reacted as in Example 12 to produce 1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-4-cis-(4-methoxyphenoxy)-L-proline.

Isomer A: yield 42% MS.

Calculated for $C_{30}H_{38}N_4O_9S \cdot 0.5 H_2O$:

C, 56.50; H, 5.80; N, 8.78.

Found:

55 C, 56.36; H, 6.12; N, 8.67.

Example 191-[1-Oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-4-cis-(4-hydroxyphenoxy)-L-proline

N-Carbobenzyloxy-4-cis-(4-t-butoxyphenoxy)-L-proline methyl ester (prepared as in Preparation 3) was reacted as in Example 13 to produce 1-[1-oxo-2-(4-nitro-1H-imidazol-1-yl)octyl]-4-cis-(4-t-butoxyphenoxy)-L-proline.

Isomer A': Yield, 34%. MS.

Calculated for $C_{27}H_{38}N_4O_7 \cdot 0.8 H_2O$:

C, 59.50; H, 7.32; N, 10.27.

Found:

C, 59.60; H, 7.04; N, 9.98.

Isomer B': Yield, 33%. MS.

Calculated for $C_{27}H_{38}N_4O_7$:

C, 61.12; H, 7.22; N, 10.56.

Found:

C, 61.37; H, 7.32; N, 10.59.

Isomer A' was further reacted as in Example 12 to produce 1-[1-Oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-4-cis-(4-t-butoxyphenoxy)-L-proline ethyl ester. The t-butoxyphenoxy proline ethyl ester was stirred in trifluoroacetic acid (TFA, 3 ml) for three hours at room temperature. The excess TFA was removed; and the residue hydrolyzed as in Example 12 to yield the product.

Isomer A: MS.

M.Pt.: 180-194°C

Calculated for $C_{29}H_{34}N_4O_9S$:

C, 56.67; H, 5.58; N, 9.12.

Found:

C, 56.95; H, 5.69; N, 8.93.

Example 201-[1-oxo-2-[4-(2-carboxy-3-hydroxybenzoyl)amino-1H-imidazol-1-yl]octyl]-4-cis-phenoxy-L-proline.

Isomer A of 1-[1-oxo-2-(4-nitro-1H-imidazol-1-yl)octyl]-4-cis-phenoxy-L-proline (1.09 mmoles, 0.5 g, prepared as in Example 12) was hydrogenated in ethanol over 5% Pd/C, filtered and concentrated. The residue was dissolved in 25 ml acetonitrile and added to a solution of 3-hydroxyphthalic anhydride in 25 ml acetonitrile. After stirring at room temperature for 2 hours, the solid was collected and dried to yield 21% ester. MS. The ester (0.24 mmoles, 0.14 g) was warmed for 15 minutes in 5 ml ethanol and 5 ml 1N NaOH, stirred at room temperature for 1 hour, and condensed. Water (20 ml) was added to the residue. The pH was adjusted to 3.0 using 5 N HCL. The precipitate was filtered and dried to yield 86% of 1-[1-oxo-2-[4-(2-carboxy-3-hydroxybenzoyl)amino-1H-imidazol-1-yl]octyl]-4-cis-phenoxy-L-proline. MS.

M.Pt.: 155-170°C.

Calculated for $C_{30}H_{34}N_4O_8$:

C, 62.27; H, 5.92; N, 9.68.

Found:

C, 62.01; H, 5.66; N, 9.62.

Example 211-[1-Oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-L-proline

Diisopropylethylamine (39.6 mmoles, 5.1 g) was added to a solution of L-proline benzyl ester hydrochloride (39.6 mmoles, 10.1 g) in 20 ml DMF at 0° and stirred for 1 hour. The solution was added to 2-(4-nitro-1H-imidazol-1-yl)octanoic acid (39.6 mmoles, 10.1 g) and hydroxybenzotriazole (43 mmoles, 5.8 g) in 10 ml DMF, and stirred for 30 minutes. Dicyclohexylcarbodiimide (43 mmoles, 8.97 g) was added portionwise over 2 hours. Ethyl acetate (50 ml) was added. The solution was filtered, dried over sodium sulfate and concentrated. The oil was chromatographed over silica gel eluted with 40% ethyl acetate in hexane to yield 5.32 g of 1-[1-oxo-2-(4-nitro-1H-imidazol-1-yl)octyl]-L-proline benzyl ester.

1-[1-Oxo-2-(4-nitro-1H-imidazol-1-yl)octyl]-L-proline benzyl ester (2.46 mmoles, 0.89 g, isomer A) was re-

duced in ethanol with 0.5 g of 10% Pd/C. The catalyst was filtered; and solution concentrated. The amine was dissolved in 5 ml of THF. Sulfolobenzoic anhydride (2.46 mmoles, 0.46 g) was added and stirred for 30 minutes. The solvent was removed; the residue triturated with ether. The solid was dissolved in 3 ml of 1N NaOH and stirred for 2 hours, acidified to pH 3.5 with 1N HCl. The product was filtered and chromatographed over reverse phase silica gel to yield 96 mg of 1-[1-oxo-2-[4-(2-sulfolobenzoyl)amino-1H-imidazol-1-yl]octyl]-L-proline. MS.

M.Pt.: 190-195°C.

Calculated. for $C_{23}H_{30}N_4O_7S$:

C, 54.53; H, 5.97; N, 11.06.

Found:

C, 54.46; H, 6.03; N, 11.08.

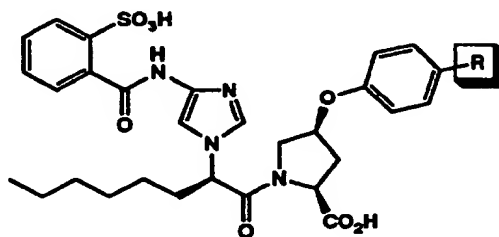
Isomer B was treated in a similar manner to yield 115 mg. MS.

M Pt. 163-170 °C.

Found:

C, 54.37; H, 6.00; N, 11.96.

The following examples were prepared in a similar manner and further illustrate the synthesis of the compounds of the invention defined by the formula:



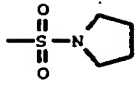
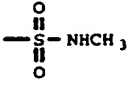
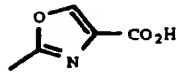
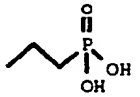
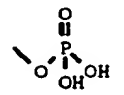
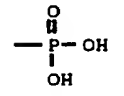
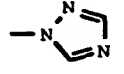
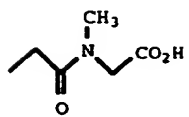
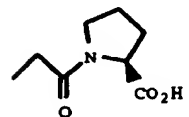
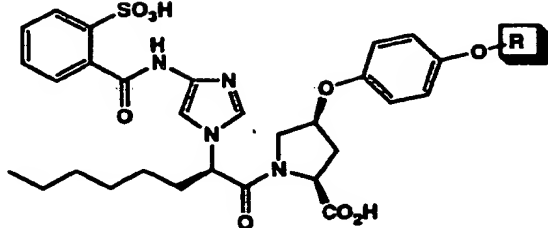
EP 0 573 271 A1

	Example	R	Yield (%)	M.P. (°C)	Elemental Analysis
5	22	Methyl	4	146-170	Calcd for $C_{30}H_{36}N_4O_8S \cdot 0.5 H_2O$: C, 58.01; H, 5.96; N, 9.02 Found: C, 58.14; H, 6.16; N, 9.32.
10	23	Ethyl	3	155-165	Calcd for $C_{31}H_{38}N_4O_8S \cdot 1.0 H_2O$: C, 57.75; H, 6.25; N, 8.68 Found: C, 57.48; H, 6.08; N, 8.80.
15	24	iPropyl	2	175-185 (dec)	Calcd for $C_{32}H_{40}N_4O_8S$: C, 59.98; H, 6.29; N, 8.74 Found: C, 59.83; H, 6.46; N, 8.51.
20	25	tButyl	3	162-270	Calcd for $C_{33}H_{42}N_4O_8S$: C, 60.53; H, 6.47; N, 8.56 Found: C, 60.92; H, 6.95; N, 7.73.
25	26	cyclopentyl	2	172-180	Calcd for $C_{34}H_{42}N_4O_8S$: C, 61.24; H, 6.35; N, 8.40 Found: C, 61.50; H, 6.47; N, 8.47.
30	27	phenyl	3	154-165	Calcd for $C_{35}H_{38}N_4O_8S$: C, 62.30; H, 5.68; N, 8.30 Found: C, 62.41; H, 5.83; N, 8.07.
35	28	F	5	150-190	Calcd for $C_{29}H_{33}F_3N_4O_8S \cdot 1.5 H_2O$: C, 55.63; H, 5.43; N, 8.90 Found: C, 55.68; H, 5.67; N, 8.42.
40	29	CF ₃	4	155-162	Calcd for $C_{30}H_{33}N_4O_8S \cdot 1.5 H_2O$: C, 51.94; H, 5.19; N, 8.00 Found: C, 52.33; H, 4.87; N, 7.64.

EP 0 573 271 A1

5	30	SCH ₃	2	162-168	Calcd for C ₃₀ H ₃₆ N ₄ O ₈ S ₂ : C, 55.89; H, 5.63; N, 8.69 Found: C, 55.68; H, 5.56; N, 8.40.
10	31	S(O)CH ₃	3	160-170	Calcd for C ₃₀ H ₃₆ N ₄ O ₈ S•1.5 H ₂ O: C, 51.94; H, 5.19; N, 8.00 Found: C, 52.33; H, 4.87; N, 7.64.
15	32	SC ₂ CH ₃	5	170-182	Calcd for C ₃₀ H ₃₆ N ₄ O ₁₀ S ₂ : C, 53.24; H, 5.36; N, 8.28 Found: C, 53.30; H, 5.52; N, 8.25.
20	33	CO ₂ H	4	185-195	Calcd for C ₃₀ H ₃₄ N ₄ O ₁₀ S•3.0 H ₂ O: C, 51.71; H, 5.78; N, 8.04 Found: C, 51.57; H, 5.47; N, 7.66.
25	34	CONH ₂	5	141-151	Calcd for C ₃₀ H ₃₅ N ₅ O ₉ S: C, 56.15; H, 5.50; N, 10.91 Found: C, 54.82; H, 5.87; N, 12.46.
30	35	CH ₂ OH	1	160-172	Calcd for C ₃₀ H ₃₆ N ₄ O ₉ S: C, 57.31; H, 5.77; N, 8.91 Found: C, 56.85; H, 5.81; N, 9.31
35					
40	36	CH ₂ CO ₂ H	5	160-175	Calcd for C ₃₁ H ₃₆ N ₄ O ₁₀ S•0.5 H ₂ O: C, 55.88; H, 5.55; N, 8.42 Found: C, 55.46; H, 5.81; N, 8.71
45	37	(CH ₂) ₂ CO ₂ H	3	140-148	Calcd for C ₃₂ H ₃₈ N ₄ O ₁₀ S: C, 57.30; H, 5.71; N, 8.35 Found: C, 57.03; H, 5.83; N, 8.29
50	38	1-imidazole	2	175-180(dec)	Calcd for C ₃₂ H ₃₆ N ₆ O ₈ S: C, 57.82; H, 5.46; N, 12.64 Found: C, 56.57; H, 5.92; N, 13.53.
55					

EP 0 573 271 A1

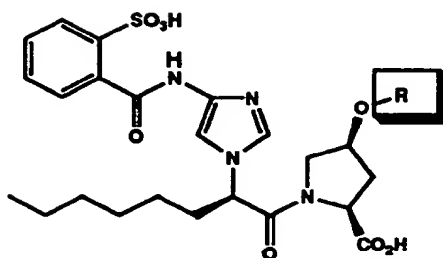
39		175-181	Calcd for $C_{33}H_{41}N_5O_{10}S_2$: C, 54.16; H, 5.65; N, 9.57. Found: C, 54.24; H, 5.90; N, 9.49
40		195-200	Calcd for $C_{30}H_{37}N_5O_{10}S_2$: C, 52.09; H, 5.39; N, 10.12. Found: C, 52.26; H, 5.56; N, 9.93.
41		165-170	Calcd for $C_{33}H_{35}N_5O_{11}S \cdot 0.25 HCl$: C, 55.14; H, 4.94; N, Found: C, 55.30; H, 5.14; N, 9.75
42		230-240 (dec)	Calcd for $C_{31}H_{39}N_4O_{11}PS \cdot 1.5 HCl$: C, 48.90; H, 5.36; N, 7.36 Found: C, 49.21; H, 5.38; N, 7.15
43		177 (dec) **	
44		185 (dec) **	
45		185°C (dec)	Calcd for $C_{31}H_{35}N_7O_8S \cdot 0.62 HCl$: C, 54.09; H, 5.22; N, 14.24 Found: C, 54.12; H, 5.25; N, 14.09.
46		157-162°C (dec)	Calcd for $C_{34}H_{41}N_5O_{11}PS$: C, 56.11; H, 5.67; N, 9.62 Found: C, 56.40; H, 5.65; N, 9.32.
47		185-190°C (dec) **	
48			

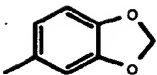
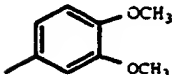
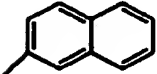
EP 0 573 271 A1

5	48	Ethyl	3	155-165	Calcd for $C_{31}H_{38}N_4O_9S \cdot 1.0 H_2O$: C, 56.3; H, 6.05; N, 8.47 Found: C, 56.6; H, 5.93; N, 8.71
10	49	iPropyl	4	138-145	Calcd for $C_{32}H_{40}N_4O_9S$: C, 58.52; H, 6.14; N, 8.53 Found: C, 58.62; H, 6.23; N, 8.45.
15	50	nButyl	2	134-155	Calcd for $C_{33}H_{42}N_4O_9S$: C, 59.09; H, 6.31; N, 8.35 Found: C, 58.85; H, 6.31; N, 8.30.
20	51	iButyl	7	160- 165(dec)	Calcd for $C_{33}H_{42}N_4O_9S \cdot 0.17 HCl$: C, 58.44; H, 6.28; N, 8.28. Found: C, 58.48; H, 6.46; N, 8.65
25	52	tButyl	3	170- 175(dec)	Calcd for $C_{33}H_{42}N_4O_9S$: C, 59.09; H, 6.31; N, 8.35 Found: C, 58.97; H, 6.22; N, 8.25
30	53	CF ₃	5	163- 165(dec)	Calcd for $C_{30}H_{33}F_3N_4O_9S$: C, 52.78; H, 4.87; N, 8.21 Found: C, 53.00; H, 5.01; N, 8.10.
35	54	cyclopentyl	7	170- 175(dec)	Calcd for $C_{34}H_{42}N_4O_9S \cdot 0.4 HCl$: C, 58.56; H, 6.13; N, 8.03. Found: C, 58.61; H, 6.05; N, 8.18.
40	55	cyclopropyl-methyl	5	163- 170(dec)	Calcd for $C_{33}H_{40}N_4O_9S$: C, 59.27; H, 6.03; N, 8.38 Found: C, 59.01; H, 5.87; N, 8.55.
45					
50					
55					

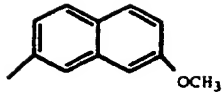
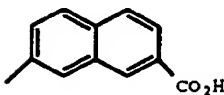
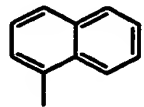
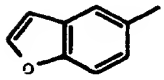
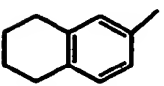
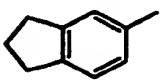
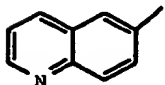
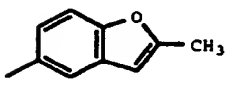
EP 0 573 271 A1

56	cyclohexyl-methyl	11	170- 174(dec)	Calcd for $C_{36}H_{46}N_4O_9S \cdot 9.73 \text{ HCl}$: C, 58.63; H, 6.39; N, 7.60. Found: C, 58.66; H, 6.13; N, 7.57.
57	CH_2CO_2H	8	161-164	Calcd for $C_{31}H_{36}N_4O_{11}S$: C, 55.35; H, 5.39; N, 9.33 Found: C, 55.51; H, 5.57; N, 8.12.
58	$C(CH_3)_2CO_2H$	1	167- 175(dec)	Calcd for $C_{33}H_{40}N_4O_{11}S \cdot 0.72 \text{ HCl}$: C, 54.55; H, 5.65; N, 7.71 Found: C, 54.43; H, 5.59; N, 8.11.

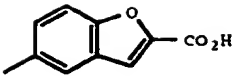
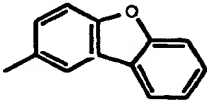
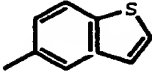
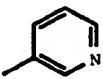
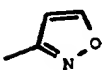


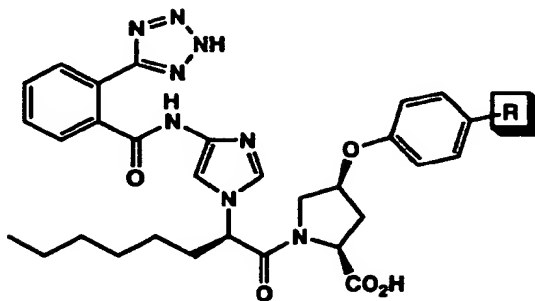
59		5	169- 175(dec)	Calcd for $C_{30}H_{34}N_4O_{10}S \cdot 0.5 \text{ HCl}$: C, 54.52; H, 5.26; N, 8.48 Found: C, 54.35; H, 5.25; N, 8.25.
60		2	152-162	Calcd for $C_{31}H_{38}N_4O_{10}S \cdot 0.5 \text{ HCl}$: C, 54.52; H, 5.26; N, 8.48 Found: C, 54.35; H, 5.25; N, 8.25.
61		5	170-175	Calcd for $C_{33}H_{36}N_4O_{10}S \cdot 0.5 \text{ H}_2O$: C, 59.37; H, 5.70; N, 8.40 Found: C, 59.06; H, 5.68; N, 8.64.

EP 0 573 271 A1

5	62		2 160-180	Calcd for $C_{14}H_{18}N_4O_9S \cdot 0.5 H_2O$: C, 59.30; H, 5.71; N, 8.14 Found: C, 59.40; H, 5.60; N, 7.89.
10	63		8 >200	Calcd for $C_{14}H_{16}N_4O_{10}S \cdot 0.75 NaCl$: C, 55.44; H, 4.92; N, 7.61 Found: C, 55.18; H, 5.05; N, 7.79.
15	64		4 170-190	Calcd for $C_{13}H_{16}N_4O_8S \cdot 1.0 H_2O$: C, 59.37; H, 5.70; N, 8.40 Found: C, 59.76; H, 5.70; N, 8.45.
20	65		1 185-190(dec)	Calcd for $C_{12}H_{15}N_5O_8S \cdot 1.0 HCl$: C, 56.01; H, 5.29; N, 10.21 Found: C, 56.38; H, 5.65; N, 10.21.
25	66		9 170-175(dec)	Calcd for $C_{12}H_{18}N_4O_8S \cdot 1.0 HCl$: C, 56.92; H, 5.82; N, 8.30 Found: C, 57.33; H, 5.84; N, 8.11.
30	67		7 175-182	Calcd for $C_{13}H_{14}N_4O_8S \cdot 0.6 HCl$: C, 58.75; H, 6.07; N, 8.30 Found: C, 58.67; H, 6.00; N, 8.53.
35	68		7 170-180(dec)	Calcd for $C_{11}H_{14}N_4O_9S \cdot 1.2 HCl$: C, 54.56; H, 5.20; N, 8.20 Found: C, 54.44; H, 5.16; N, 8.44.
40	69		6 170-178(dec)	Calcd for $C_{13}H_{10}N_4O_9S \cdot 0.5 HCl$: C, 57.28; H, 5.48; N, 8.48 Found: C, 57.27; H, 5.49; N, 8.35.
45				
50				
55				

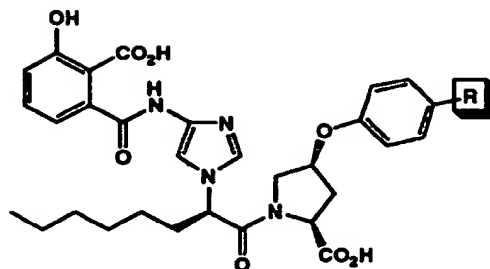
EP 0 573 271 A1

70		3	193- 200(dec)	Calcd for $C_{10}H_8O_3$: C, 56.30; H, 5.02; N, 8.21 Found: C, 56.19; H, 5.10; N, 8.21.
71		14	173- 180(dec)	Calcd for $C_{15}H_{12}O$: C, 59.45; H, 5.20; N, 7.92 Found: C, 59.36; H, 5.38; N, 8.20.
72		3	168- 172(dec)	Calcd for $C_{10}H_8S$: C, 47.59; H, 4.83; N, 7.16 Found: C, 47.52; H, 4.63; N, 7.32.
73		3	180- 183(dec)	Calcd for C_7H_7N : C, 47.43; H, 4.88; N, 9.90 Found: C, 47.01; H, 4.88; N, 10.49.
74		6	225- 230(dec)	Calcd for C_4H_5NO : C, 50.62; H, 5.19; N, 11.35 Found: C, 50.62; H, 5.18; N, 11.19.
75	OMethyl	3	160-170	Calcd for $C_{31}H_{36}N_8O_6 \cdot 1.5 H_2O$: C, 57.80; H, 6.10; N, 17.40 Found: C, 57.68; H, 5.75; N, 17.32.



EP 0 573 271 A1

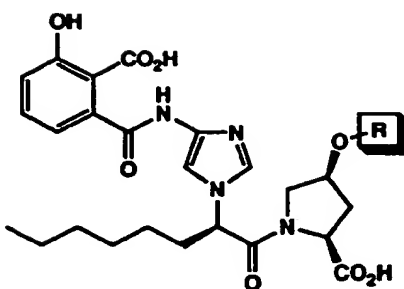
76	OtButyl	17	149-	Calcd for $C_{34}H_{42}N_8O_6 \cdot 0.5 HCl$:
5			156(dec)	C, 60.32; H, 6.33; N, 16.55
				Found: C, 60.46; H, 6.22; N, 16.69.
77	CH_2CO_2H	5	135-146	Calcd for $C_{32}H_{36}N_8O_7 \cdot 1.0 H_2O$:
10				C, 57.90; H, 5.70; N, 16.90
				Found: C, 57.87; H, 5.81; N, 15.40.
78	CO_2H	5	157-178	Calcd for $C_{31}H_{34}N_8O_7$:
15				C, 59.04; H, 5.43; N, 17.77
				Found: C, 58.88; H, 5.54; N, 17.54.
79	OCH_2CO_2H	4	175-190	Calcd for $C_{32}H_{36}N_8O_8 \cdot 1.5 H_2O$:
20				C, 55.89; H, 5.72; N, 16.29
				Found: C, 55.64; H, 5.37; N, 16.18.

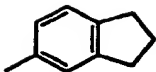
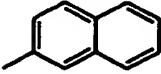
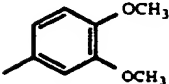


80	Ethyl	2	133-143	Calcd for $C_{30}H_{38}N_4O_8 \cdot 1 H_2O$:
40				C, 61.5; H, 6.45; N, 8.97; .
				Found: C, 61.0; H, 6.29; N, 9.05
81	OH	1	135-	Calcd for $C_{30}H_{34}N_4O_9$
45			140(dec)	C, 60.60; H, 5.76; N, 9.42
				Found: C, 48.81; H, 4.65; N, 7.14.

EP 0 573 271 A1

82	OMethyl	4	127-135	Calcd for $C_{31}H_{36}N_4O_9 \cdot 1.0 H_2O$: C, 59.41; H, 6.06; N, 8.94 Found: C, 59.41; H, 5.96; N, 9.05.
83	OEthyl	5	133-137	Calcd for $C_{32}H_{38}N_4O_9 \cdot 1.0 H_2O$: C, 59.93; H, 6.24; N, 8.74 Found: C, 60.06; H, 6.14; N, 9.15.
84	OnButyl	2	145-151	Calcd for $C_{34}H_{42}N_4O_9 \cdot 1.5 H_2O$: C, 60.26; H, 6.60; N, 8.26 Found: C, 59.97; H, 6.28; N, 7.95.
85	CO ₂ H	3	155-160	Calcd for $C_{31}H_{34}N_4O_{10} \cdot 2.0 H_2O$: C, 56.52; H, 5.81; N, 8.50 Found: C, 56.78; H, 5.49; N, 8.47.
86	CH ₂ CO ₂ H	3	123-134	Calcd for $C_{32}H_{36}N_4O_{10}$: C, 60.37; H, 5.70; N, 8.80 Found: C, 60.11; H, 5.82; N, 8.76.
87	CN	3	141-151	Calcd for $C_{31}H_{33}N_5O_8 \cdot 1.5 H_2O$: C, 59.04; H, 5.75; N, 11.10 Found: C, 59.27; H, 5.72; N, 11.42.



88		9 148-153	Calcd for $C_{13}H_{18}N_4O_8 \cdot 0.75 HCl$: C, 61.35; H, 6.05; N, 8.67 Found: C, 61.30; H, 6.01; N, 8.64.
89		2 146-152	Calcd for $C_{14}H_{16}N_4O_8 \cdot 0.5 H_2O$: C, 64.04; H, 5.84; N, 8.78 Found: C, 63.98; H, 5.77; N, 8.65
90		4 130-135	Calcd for $C_{12}H_{18}N_4O_{10}$: C, 58.52; H, 6.13; N, 8.53 Found: C, 58.30; H, 5.98; N, 8.40

Example 91

1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-4-cis-(4-methyleneophosphonic acid)-phenoxy)-L-proline

To a solution of dimethylphosphite (22.4 mL, 244 mmol) in 400 mL of anhydrous THF at 0°C was added NaH (9.3 g, 232 mmol, 60% dispersion in mineral oil) in small portions. Benzyloxybenzylchloride (53.7 g, 232 mmol) was then introduced via canula as a solution in 100 mL of anhydrous THF. The resulting mixture was warmed to room temperature and stirred overnight. The solvent was then removed *in vacuo* and the resulting oil was partitioned between H₂O/ether (300 mL ea.). The layers were separated, and the aqueous extracted with ether (2x200 mL). The organic was combined, dried (Na₂SO₄) and concentrated to give 78 g of a thick oil. Chromatography (SiO₂, 75% ethyl acetate/25% hexane) provided 36.6 g (52%) of dimethyl-(4-benzyloxy)-benzylphosphonate as a solid residue. MS.

Calculated for C₁₈H₁₉O₄P:

C, 62.74; H, 6.25.

Found:

C, 62.96; H, 6.23.

A solution of dimethyl-(4-benzyloxy)-benzylphosphonate (19.4 g, 63 mmol) in 100 mL of 1% con. HCl in ethanol was treated with 840 mg of 5% Pd/C. The mixture was hydrogenated at 40 psi for 30 minutes. The reaction mixture was then filtered through a pad of celite, and the filtrate concentrated *in vacuo* to give 13.6 g (100 %) of dimethyl-(4-hydroxy)-benzylphosphonate as a white solid. M.Pt. 126-129°C.

Calculated for C₉H₁₃O₄P:

C, 50.01; H, 6.06.

Found:

C, 50.21; H, 6.09.

To a solution of N-carbobenzyloxy-trans-4-hydroxyproline methyl ester (10.0 g, 35.8 mmol) in 400 mL of anhydrous THF under N₂ at 0°C was added triphenylphosphine (10.6 g, 39.4 mmol) and dimethyl-(4-hydroxy)-benzylphosphonate (7.9 g, 37.8 mmol). To this mixture was added diethyl azodicarboxylate (6.3 mL, 39.4 mmol) dropwise over a 30 minute period. The reaction mixture was then allowed to warm to room temperature and stirred for 18 hours. The solvent was then removed *in vacuo* and the residue was chromatographed (SiO₂, 50-100% ethyl acetate/hexane) to give 13.3 g (75%) of N-carbobenzyloxy-4-(cis)-(dimethyl-4-oxobenzyl phosphonate)-L-proline methyl ester as a thick oil.

Calculated for C₂₃H₂₈NO₈P:

C, 57.86; H, 5.91; N, 2.93.

Found:

C, 57.66; H, 6.04; N, 3.02.

A solution of N-carbobenzyloxy-4-(cis)-(dimethyl-4-oxobenzylphosphonate)-L-proline methyl ester (6.6 g, 13.8 mmol) in 100 mL of 1% concentrated HCl in ethanol was treated with 1.0 g of 10% Pd/C. The mixture was hydrogenated at 40 psi for 2 hours and then passed through a pad of celite to remove the catalyst. The filtrate

was concentrated to an oil and then partitioned between CHCl_3 and saturated NaHCO_3 (100 mL each). The layers were separated and the organic was dried (Na_2SO_4), and concentrated *in vacuo* to give the crude de-protected proline ester as a pale yellow oil.

5 In a separate flask, 2-(4-nitroimidazole)-octanoic acid (3.7 g, 14.5 mmol) was dissolved in 25 mL of anhydrous CH_2Cl_2 . To this solution was added oxalyl chloride (1.7 mL, 18.9 mmol) followed by 3 drops of DMF. When gas evolution ceased, the solvent was removed *in vacuo* to give the acid chloride as an amber oil that was evaporated from an additional 20 mL of CH_2Cl_2 . The acid chloride was used immediately in the next reaction.

To a solution of the above proline ester in 20 mL of anhydrous CH_2Cl_2 at 10°C was added N,N-diisopropylethylamine (2.7 mL, 15.1 mmol). The acid chloride was then introduced dropwise from an addition funnel as a solution in 10 mL of CH_2Cl_2 . The resulting mixture was warmed to room temperature and stirred for 18 hours. The reaction was next distributed between ethyl acetate/ H_2O (200 mL ea.). The layers were separated and the aqueous extracted with ethyl acetate (3x100 mL). The organic was combined and washed with brine followed by H_2O . The organic was then dried (Na_2SO_4) and concentrated *in vacuo* to give as 1-[1-oxo-2-(4-nitro-1H-imidazol-1-yl)octyl]-4-cis-[(4-dimethylmethylenephosphonate)-phenoxy]-L-proline methyl ester an oil. The diastereomeric octanoamides were separated by chromatography (SiO_2 , 1% methanol/ethyl acetate to give 1.57 g (19%) of the (R,S,S) isomer and 1.225 g of the (S,S,S) isomer along with 1.12 g of a mixed fraction. Data for (R,S,S) isomer: MS.

Calculated for $\text{C}_{26}\text{H}_{37}\text{N}_4\text{O}_9\text{P}$:

20 C, 53.79; H, 6.42; N, 9.65

Found:

C, 53.26; H, 6.58; N, 9.18.

Data for (S,S,S) isomer:

MS.

25 Calculated for $\text{C}_{26}\text{H}_{37}\text{N}_4\text{O}_9\text{P}$:

C, 53.79; H, 6.42; N, 9.65

Found:

C, 53.55; H, 6.47; N, 9.38.

To a solution of 4-nitroimidazole octanoamide (4.0 g, 6.9 mmol) in 50 mL of absolute ethanol was added 30 1.0 g of 5% Pd/C. The mixture was hydrogenated at 40 psi for 30 minutes. The catalyst was then removed by passing the mixture through a pad of celite. The filtrate was concentrated to an amber oil that was azeotroped 2x from anhydrous THF.

In a separate flask, sulfobenzoic anhydride (1.4 g, 7.6 mmol) was dissolved in 5 mL of anhydrous THF under N_2 . To this solution was added the above aminoimidazole as a solution in 5 mL of anhydrous THF. After stirring 35 for 30 minutes, the solution was triturated with ether/hexanes to yield 4.70 g (93%) of the sulfonic acid as a light yellow solid that was collected by filtration. This product, 1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-4-cis-[(4-dimethylmethylenephosphonate)-phenoxy]-L-proline methyl ester, was used in the next reaction without further purification. M.Pt. 110°C (decomp). MS.

Calculated for $\text{C}_{33}\text{H}_{43}\text{N}_4\text{O}_{11}\text{PS}$:

40 C, 53.94; H, 5.90; N, 7.62

Found:

C, 53.66; H, 5.94; N, 6.85.

To a solution of the above methyl ester (4.70 g, 6.5 mmol) in 25 mL of anhydrous CH_2Cl_2 at 0°C was added 45 trimethylsilylbromide (5.0 g, 32.4 mmol) dropwise over a 15 minute period. The resulting mixture was warmed to room temperature and stirred for 1 hour. The solvent was then removed *in vacuo*, and the residue dissolved in 16 mL of 2N NaOH. After stirring for 1 hour, the reaction mixture was acidified to pH = 1.0 with 5N HCl. The aqueous was extracted with 10% ethanol/ethyl acetate (3x50 mL). The organic was dried (Na_2SO_4) and concentrated to give a solid residue that was dissolved in minimal absolute ethanol and triturated with ether/hexanes. Isolation by filtration provided 2.79 g (61%) of the title phosphonic acid as a pale yellow solid.

50 M.Pt. 190°C (decomp). MS.

Calculated for $\text{C}_{30}\text{H}_{37}\text{N}_4\text{O}_{11}\text{PS}$:

C, 52.02; H, 5.38; N, 8.09

Found:

C, 51.80; H, 5.42; N, 7.91.

55

Exempl 92

1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-4-cis-[(4-N-methanesulfonamido)-phenoxy]-L-proline.

To a solution of N-Boc-*trans*-4-hydroxyproline methyl ester (10.0 g, 41 mmol) 150 mL of anhydrous THF at 0°C under N₂ was added triphenylphosphine (12.7 g, 48 mmol) and 4-nitrophenol (6.7 g, 48 mmol). To this mixture was added diethylazodicarboxylate (7.7 mL, 48 mmol) dropwise over a 30 minute period. The mixture was warmed to room temperature. After stirring for 2 days, the solvent was removed *in vacuo*, and the crude oil treated successively with 200 mL portions of toluene and ether to remove triphenylphosphine oxide and diethylazodihydrazide by crystallization. The resulting oil was then chromatographed (SiO₂, 15-50% ethyl acetate/hexanes) to provide 5.2 g (34%) of N-Boc-4-(*cis*)-(4-nitrophenoxy)-L-proline methyl ester as a light yellow oil.

Calculated for C₁₇H₂₂N₂O₇:

C, 55.73; H, 6.05; N, 7.65

Found:

C, 55.94; H, 6.09; N, 7.59.

To a solution of N-Boc-4-(*cis*)-(4-nitrophenoxy)-L-proline methyl ester (9.0 g, 24.7 mmol) in 100 mL of ethanol was added 1.5 g of 10% Pd/C. This mixture was hydrogenated for 3 hours at 40 psi. The catalyst was then removed by passing the reaction through a pad of celite. Concentration *in vacuo* gave an oil that was used immediately in the next reaction.

The above oil was dissolved in 50 mL of anhydrous CH₂Cl₂ along with 11.5 mL (65.5 mmol) of N,N-diisopropylethylamine. To this mixture was added methanesulfonyl chloride (6.4 g, 55 mmol) dropwise via an addition funnel as a solution in 10 mL of CH₂Cl₂. After stirring for 2 hours, the reaction was poured into H₂O (200 mL). The aqueous was extracted with ethyl acetate (3x100 mL). The organic was dried (Na₂SO₄) and concentrated *in vacuo* to an oil. Chromatography (SiO₂, 25% ethyl acetate/hexanes) provided 3.22 g (27%) of N-Boc-4-(*cis*)-[(4-N,N-bismethanesulfonamido)-phenoxy]-L-proline methyl ester as a colorless oil.

Calculated for C₁₉H₂₈N₂O₉S₂:

C, 46.33; H, 5.73; N, 5.69

Found:

C, 46.16; H, 5.48; N, 5.45.

To a solution of N-Boc-4-(*cis*)-[(4-N,N-bismethanesulfonamido)-phenoxy]-L-proline methyl ester (3.0 g, 6.1 mmol) in 40 mL of anhydrous CH₂Cl₂ at room temperature was added trifluoroacetic acid (1.5 mL, 18 mmol). After stirring for 3 hours, the solvent was removed *in vacuo* to give an oil that was partitioned between saturated NaHCO₃ solution and ethyl acetate (100 mL ea.). The organic was dried (Na₂SO₄) and concentrated to yield 2.27 g (94%) of 4-(*cis*)-[(4-N,N-bismethanesulfonamido)-phenoxy]-L-proline methyl ester as a solid that was used immediately in the next reaction.

2-(4-Nitroimidazole)-octanoic acid (1.7 g, 6.7 mmol) was converted to the acid chloride and reacted with the above proline ester using the previously described method. Chromatography (SiO₂, 70-100% ethyl acetate/hexanes) of the crude reaction mixture provided 1.66 g (43%) of the (R)-1-[1-oxo-2-(4-nitro-1H-imidazol-1-yl)octyl]-4-(*cis*)-[(4-N,N-bismethanesulfonamido)-phenoxy]-L-proline methyl ester as a white solid. M.P. 106-109.

Calculated for C₂₅H₃₅N₅O₁₀S₂:

C, 47.69; H, 5.60; N, 11.12

Found:

C, 47.88; H, 5.51; N, 11.22.

To a solution of (R)-1-[1-oxo-2-(4-nitro-1H-imidazol-1-yl)octyl]-4-(*cis*)-[(4-N,N-bismethanesulfonamido)-phenoxy]-L-proline methyl ester (1.26 g, 2.0 mmol) in 50 mL of absolute ethanol was added 0.5 g of 5% Pd/C. The mixture was hydrogenated at 40 psi for 1.5 hours. The catalyst was then removed by passing the mixture through a pad of celite. The filtrate was concentrated to an amber oil that was azeotroped 2x from anhydrous THF.

In a separate flask, sulfobenzoic anhydride (0.40 g, 2.2 mmol) was dissolved in 5 mL of anhydrous THF under N₂. To this solution was added the above aminoimidazole as a solution in 5 mL of anhydrous THF. After stirring for 30 minutes, the solution was triturated with ether/hexanes to yield 1.50 g (95%) of (R)-1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-4-(*cis*)-[(4-N,N-bismethanesulfonamido)-phenoxy]-L-proline methyl ester, as a light yellow solid that was collected by filtration. This intermediate was used in the next reaction without further purification. M.P. 165-170°C. MS.

Calculated for C₃₂H₄₁N₅O₁₂S₃·1.0 H₂O:

C, 47.93; H, 5.40; N, 8.73.

F und:

C, 48.31; H, 5.40; N, 8.44.

5 (R)-1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-4-(cis)-[(4-N,N-bismethanesulfonamido)-phenoxy]-L-proline methyl ester (0.40 g, 0.52 mmol) was dissolved in a solution of 1 N NaOH (3 mL) and THF (2 mL) at room temperature. The solution was stirred overnight. The pH was then adjusted to 1.0 with 1 N HCl. A precipitate formed that was extracted from the aqueous using 10% ethanol/ethyl acetate. Drying (Na₂SO₄) and concentration in vacuo gave a solid residue that was triturated from MeOH/ether to yield 0.27 g (75%) of (R)-1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-4-(cis)-[(4-N-methanesulfonamido)-phenoxy]-L-proline as a white solid. M.Pt. 195-198°C. MS.

Calculated for C₃₀H₃₇N₅O₁₀S₂:

C, 52.09; H, 5.39; N, 10.12.

Found:

15 C, 51.82; H, 5.47; N, 10.28.

Example 93

20 (R)-1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-4-(cis)-[(4-N-trifluoromethanesulfonamido)-phenoxy]-L-proline

Prepared in a manner analogous to Example 92 was (R)-1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-4-(cis)-[(4-N-trifluoromethanesulfonamido)-phenoxy]-L-proline. MP 145 °C (dec). MS.

Calculated for C₃₀H₃₃N₅O₁₀S₂F₃·1.0 NaCl:

25 C, 46.93; H, 4.84; N, 9.99.

Found:

C, 46.97; H, 4.58; N, 9.75.

Example 94

30 (R)-1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-4-(cis)-[(4-N,N-methyl-methanesulfonamido)-phenoxy]-L-proline.

35 To a solution of 4-benzyloxyaniline (21.7 g, 108 mmol) in 100 mL of anhydrous CH₂Cl₂ was added N,N-diisopropylethylamine (31.0, 42.5 mmol). The mixture was then cooled to 10°C and treated with methanesulfonyl chloride (18.2 mL, 234 mmol). After stirring for 1 hour, the reaction was distributed between H₂O/ethyl acetate. A solid formed that was collected by filtration. Drying in vacuo provided 25.7 g (68%) of 4-benzyloxy-N,N-bismethanesulfonamido-benzene as a brown solid. M.Pt. 212-215 °C. MS.

Calculated for C₁₆H₁₇NO₅S₂:

40 C, 50.69; H, 4.82; N, 3.94.

Found:

C, 50.87; H, 4.85; N, 3.91.

45 To a solution of 4-benzyloxy-N,N-bismethanesulfonamido-benzene (25.0 g, 71.0 mmol) in 300 mL of THF was added 1 N NaOH (250 mL). The resulting solution was stirred for 2 hours at 70°C. Upon cooling, the mixture was acidified to pH = 1.0 with 5 N HCl. Extraction with CHCl₃ (5x250 mL), followed by drying (Na₂SO₄) and concentration in vacuo provided 15.05 g (51%) of 4-benzyloxy-N-methanesulfonamido-benzene as a white solid. M.Pt. 155-158 °C. MS.

Calculated for C₁₄H₁₅NO₃S:

C, 60.63; H, 5.45; N, 5.05.

50 Found:

C, 60.59; H, 5.46; N, 5.01.

55 To a solution of the above compound (15.0 g, 55.0 mmol) in 45 mL of anhydrous DMF was added K₂CO₃ (15.3 g, 110 mmol). To this mixture was added MeI (11.8 g, 83.0 mmol). After stirring at room temperature for 18 h a precipitate formed that was collected by first diluting the reaction with H₂O, following by vacuum filtration. Drying in vacuo yielded 15.7 g (97%) of 4-benzyloxy-N,N-methyl-methanesulfonamido-benzene as a white solid. M.Pt. 175-178 °C. MS.

Calculated for C₁₆H₁₇NO₃S:

C, 61.83; H, 5.88; N, 4.81.

Found:

C, 62.04; H, 5.96; N, 4.97.

To a solution of 4-benzyloxy-N,N-methyl-methanesulfonamido-benzene (14.0 g, 48 mmol) in 100 mL of ethanol was added 4.0 g of 5 % Pd/C. The mixture was hydrogenated at 40 psi for 2 hours. The reaction was then passed through a pad of celite, and the filtrate concentrated *in vacuo* to give 9.93 g (100%) of 4-N,N-methyl-methanesulfonamidophenol as a white solid. M.Pt. 117-120 °C. MS.

Calculated for $C_8H_{11}NO_3S$:

C, 47.75; H, 5.51; N, 6.96.

Found:

C, 47.65; H, 5.28; N, 6.88.

This material was employed analogous to Example 92 to prepare the titled compound.

Example 95

(R)-1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-4-(cis)-[(4-(methylene-N-methanesulfonamido))-phenoxy]-L-proline.

To a solution of N-carbobenzyloxy-*trans*-4-hydroxy-L-proline methyl ester (10.0 g, 35.8 mmol) in 200 mL of anhydrous THF under N_2 was added triphenylphosphine (10.6 g, 39.4 mmol) and 4-cyanophenol (4.7 g, 39.4 mmol). This solution was cooled to 0°C and then treated with diethylazodicarboxylate (6.3 mL, 39.4 mmol), added dropwise over 30 minutes. The reaction was warmed to room temperature and stirred for 2 days. The solvent was removed *in vacuo* and the residue chromatographed (SiO_2 , 30% ethyl acetate/hexanes) to provide 12.1 g (89%) of N-carbobenzyloxy-4-(cis)-(4-cyanophenoxy)-L-proline methyl ester as a colorless oil. MS.

Calculated for $C_{21}H_{20}N_2O_6$:

C, 66.31; H, 5.30; N, 7.36.

Found:

C, 66.10; H, 5.34; N, 7.50.

To a solution of N-carbobenzyloxy-4-(cis)-(4-cyanophenoxy)-L-proline methyl ester (3.8 g, 10 mmol) in 75 mL of methanol was added $COCl_2$ (2.6 g, 20 mmol). This solution was cooled to 0°C and then treated with $NaBH_4$ (3.8 g, 100 mmol), added in small portions. After stirring for 2 hours, 50 mL of 3 N HCl were added. After stirring this solution for 15 minutes, the reaction was distributed between H_2O /ether (200 mL ea.). The layers were separated, and the aqueous phase was extracted with ether (2x100 mL). The aqueous was then made basic with concentrated NH_4OH solution. Extraction with ethyl acetate (3x 100 mL), followed by drying (Na_2SO_4) and concentration *in vacuo* provided 3.50 g (90%) of N-carbobenzyloxy-4-(cis)-[(4-aminomethyl)-phenoxy]-L-proline methyl ester as an oil. This material was used in the next reaction without further purification. MS.

Calculated for $C_{21}H_{24}N_2O_6$:

C, 65.61; H, 6.29; N, 7.29.

Found:

C, 65.87; H, 6.04; N, 7.03.

To a solution of N-carbobenzyloxy-4-(cis)-[(4-aminomethyl)-phenoxy]-L-proline methyl ester (0.90 g, 2.34 mmol) in 15 mL of anhydrous CH_2Cl_2 was added N,N-diisopropylamine (0.6 mL, 3.4 mmol). This solution was cooled to 0°C and then treated with methanesulfonylchloride (0.22 mL, 2.8 mmol), added as a solution in 5 mL of CH_2Cl_2 . After stirring for 1.5 hours, the reaction was distributed between ethyl acetate/ H_2O (50 mL ea.). The layers were separated, and the aqueous was extracted with ethyl acetate (2x50 mL). The organic was dried (Na_2SO_4) and concentrated *in vacuo* to give a crude oil. Chromatography (SiO_2 , 50/50 ethyl acetate/hexanes) provided 0.74 g (70%) of N-carbobenzyloxy-4-(cis)-[(4-(methylene-N-methanesulfonamido))-phenoxy]-L-proline methyl ester as a colorless oil. MS.

To a solution of (-)-cinchonidine (48.0 g, 163 mmol) in 880 mL of distilled H_2O at room temperature was added 2-(4-nitro-1H-imidazol-1-yl)-octanoic acid (83.0 g, 326 mmol) as a solution in 440 mL of ethanol. To this mixture was added triethylamine (11.7 mL). The mixture was then heated to 80°C, and the pH was maintained between 6.9 and 7.1 by the dropwise addition of triethylamine (5- 10 mL). After the pH stabilized at 7.01, the solution was allowed to cool to room temperature, and let stand overnight whereupon crystallization of the (R)-2-(4-nitro-1H-imidazol-1-yl)-octanoic acid-cinchonidine salt occurred. The crystalline salt was collected by filtration. The salt was then suspended in 200 mL ea. of ethyl acetate/ H_2O . To this suspension was added 1N HCl (750 mL). The layers were separated, and the aqueous was extracted with ethyl acetate (2x500 mL). The organic was combined, dried (Na_2SO_4), and concentrated *in vacuo* to provide 29.9 g (72%) of (R)-2-(4-nitro-1H-imidazol-1-yl)-octanoic acid as an off-white solid. M.Pt. 116-118°C.

Calculated for $C_{11}H_{17}N_3O_4$:

C, 51.76; H, 6.71; N, 16.46.

Found:

C, 51.89; H, 6.76; N, 16.20. $[\alpha]_D -29.9$ (c 1.00, ethanol).

5 Enantiomeric excess was determined to be 96% by conversion of the acid to its methyl ester (diazomethane), followed by HPLC analysis employing a chiral column.

(R)-2-(4-Nitro-1H-imidazol-1-yl)-octanoic acid (16.0 g, 63.0 mmol) was dissolved in 1 L of anhydrous methanol. To this solution was added pTsOH (300 mg). The reaction was then heated to reflux for 16 hours. Upon cooling, the solvent was removed in vacuo, to give an oil that was dissolved in 300 mL of ethyl acetate. The solution was washed (2x250 mL) with saturated NaHCO₃ solution. The organic was then dried (Na₂SO₄) and concentrated in vacuo to provide 13.2 g (78%) of (R)-methyl-2-(4-nitro-1H-imidazol-1-yl)-octanoate as an amber oil.

Calculated for C₁₂H₁₉N₃O₄:

C, 53.32; H, 7.11; N, 15.60.

15 Found:

C, 53.23; H, 7.05; N, 15.39.

(R)-Methyl-2-(4-nitro-1H-imidazol-1-yl)-octanoate (13.0 g, 45.7 mmol) was dissolved in 150 mL of absolute ethanol. To this solution was added 2.0 g of 10% Pd/C. The mixture was hydrogenated at 40 psi for 2 hours. The catalyst was then removed by passing the reaction through a pad of celite. The filtrate was then concentrated to an oil that was evaporated twice from anhydrous THF (100 mL). The crude product was then dissolved in 100 mL of anhydrous THF and treated with KOAc (4.44 g) and K₂CO₃ (3.12 g). To this mixture was added sulfobenzoyl anhydride (8.83 g, 47.7 mmol). The reaction was stirred for 4 hours after which time a precipitate formed. The mixture was diluted with THF (100 mL) and the solid collected by filtration. Drying in vacuo provided 22.5 g of crude (R)-methyl-[(2-sulfobenzoyl)amino-1H-imidazol-1-yl]-octanoate-potassium salt. This material was carried on to the next reaction without further purification.

The potassium salt (22.5 g) was dissolved in a mixture of 200 mL H₂O and 100 mL of ethanol. To this solution was added 1N NaOH (53 mL). The reaction was allowed to stir for 3 hours. Ethanol was then removed in vacuo, and the aqueous acidified to pH = 1.5 with 5N HCl. This solution was extracted with 10% ethanol/ethyl acetate (3x200 mL). The organic was dried (Na₂SO₄) and concentrated in vacuo to give 8.65 g (46% for two steps) of (R)-[(2-sulfobenzoyl)amino-1H-imidazol-1-yl]-octanoic acid as a white solid. MS.

Calculated for C₁₈H₂₃N₃O₆S:

C, 52.80; H, 5.66; N, 10.26.

Found:

C, 52.53; H, 5.59; N, 10.27.

35 To a solution of N-carbobenzoyloxy-4-(cis)-[(4-(methylene-N-methanesulfonamido))-phenoxy]-L-proline methyl ester (1.5 g, 3.25 mmol) in 50 mL of absolute ethanol was added 0.5 g of 5% Pd/C. This mixture was hydrogenated at 40 psi for 1.5 hours. The reaction mixture was then passed through a pad of celite, and the filtrate concentrated in vacuo to give 1.07 g of 4-(cis)-[(4-(methylene-N-methanesulfonamido))-phenoxy]-L-proline methyl ester as an oil. MS. This material was used immediately in the next reaction.

40 To a solution of the above amine in 10 mL of anhydrous DMF was added (R)-[(2-sulfobenzoyl)amino-1H-imidazol-1-yl]-octanoic acid (1.00 g, 2.45 mmol) and hydroxybenzotriazole (0.37 g, 2.77 mmol). This mixture was cooled to 0°C, and then treated with dicyclohexylcarbodiimide (0.56 g, 2.70 mmol). The resulting solution was warmed to room temperature and stirred for 48 hours. After removal of dicyclohexylurea by filtration, the filtrate was diluted with 100 mL of ethyl acetate and washed several times with H₂O. The organic was then dried (Na₂SO₄) and concentrated in vacuo to an oil. Chromatography (SiO₂, 5% methanol/CHCl₃) provided 0.84 g (34%) of (R)-1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-4-(cis)-[(4-(methylene-N-methanesulfonamido))-phenoxy]-L-proline methyl ester as a white solid. M.Pt. 150 (dec).

Calculated for C₃₂H₄₁N₅O₁₀S₂:

C, 53.40; H, 5.74; N, 9.73.

50 Found:

C, 53.66; H, 5.97; N, 9.50.

(R)-1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-4-(cis)-[(4-(methylene-N-methanesulfonamido))-phenoxy]-L-proline methyl ester (0.37 g, 0.52 mmol) was dissolved in a mixture of 1N NaOH (3.0 mL) and THF (7 mL). This solution was stirred for 1 hour. The THF was then removed in vacuo, and the aqueous was acidified to pH = 1.0 using 1 N HCl. Extraction with 5% ethanol/ethyl acetate (2x) followed by drying (Na₂SO₄) of the organic and concentration yielded a solid residue. Trituration from ethanol/ethyl acetate-ether provided 0.26 g (74%) of (R)-1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl]-4-(cis)-[(4-(methylene-N-methanesulfonamido))-phenoxy]-L-proline as an off-white solid. M.Pt. 172-176.

Calculated for C₃₁H₃₉N₅O₁₀S₂:

C, 52.75; H, 5.57; N, 9.92.

Found:

C, 52.54; H, 5.53; N, 10.15.

- 5 As previously discussed, the compounds of Formula I are potent effective antagonists of angiotensin II. The ability of representative compounds of Formula I to block angiotensin II receptor binding was determined using the adrenal glomerulosa assay. The ability to antagonize angiotensin-induced vasoconstriction was evaluated in the rabbit aorta test system.

10 Adrenal Glomerulosa Test System

Binding of I^{125} -angiotensin II to adrenal membranes was routinely carried out in 96-well filtration plates. Adrenal membranes were prepared from the capsular portion (glomerulosa layer attached) of rat adrenal glands by differential centrifugation. Briefly, capsules were homogenized in a solution containing sucrose, 250
15 mM; $MgCl_2$, 1 mM; and tris, 5 mM at pH 7.5 and 4°C using a polytron at setting 5 for 20 seconds. The homogenate was stirred, gently, for 15 minutes at 4°C and then centrifuged 10 minutes, at 1000 x g, 4°C. The supernatant was centrifuged 30 minutes, at 30,000 x g, 4°C, and the resulting pellet resuspended in 50 mM tris. Membrane preparations were stored in aliquots at -70°C until used. Binding of I^{125} -angiotensin II to adrenal membranes was performed at room temperature for 90 minutes in 96-well plates containing a hydrophilic poly-
20 vinylidene fluoride membrane (0.45 μ m, Millipore-GV multiscreen). Each 250 μ l incubate contained the following (final concentration): tris, 50 mM; NaCl, 120 mM; $MgCl_2$, 5 mM; dithiothreitol 1 mM; bovine serum albumin, 0.05%; I^{125} -angiotensin II, 0.1 nM; and adrenal membrane protein, 8-15 μ g. Antagonists were added in concentrations from 10 nM to 100 μ M. Non-specific binding was measured in the presence of 0.1 μ M Sar₁, Ile₈ angiotensin II.

25 Binding was terminated by vacuum filtration. Receptor-ligand complex trapped on filters was washed 3 times with 300 μ l ice-cold wash solution (tris, 50 mM; NaCl, 120 mM; $MgCl_2$, 5 mM; dithiothreitol, 1 mM). Filter discs were dried, punched out and counted in a gamma counter at 52% efficiency. Specific binding represented 96% of total binding (approximately 150 fmol angiotensin II/mg protein). The molar concentration (IC_{50}) of the inhibitor that displaced 50% of the binding of I^{125} angiotensin II for each compound was calculated using a 4
30 parameter logistics model (NonLin, SAS Institute). Data are expressed as K_i calculated using the Cheng Prusoff equation. See Cheng et al. Biochem. Pharmacol. 22: 3099 (1973).

Rabbit Aorta Test System

35 New Zealand white rabbits (Hazelton, 2-3 kg) were sacrificed by cervical dislocation. The thoracic aortas were removed and cleaned of excess fat and connective tissue. Rings of tissue (3 mm wide) were mounted in 10 ml tissue baths between 2 L-shaped stainless steel hooks. The lower hook was attached to a stationary rod. The upper hook was attached to a force displacement transducer (Grass model FT.03). The bath chambers were maintained at 37°C, aerated with 95% O₂/5% CO₂, and contained physiological solution of the following
40 composition (mM): NaCl, 117; glucose, 5.6; NaH₂PO₄, 1.0; MgSO₄, 0.7; KCl, 5.2; CaCl₂, 1.8; NaHCO₃, 26; and phenolamine HCl, 0.003.

Rings were equilibrated for 1 hour with 2 g of tension. During the equilibration period, the tissues were washed by overflow every 15 minutes. Rings were then exposed to 10⁻⁸ M angiotensin II (All) and were allowed to contract until a steady state was reached. Tissues were then washed every 15 minutes for 1 hour. This was
45 repeated every hour until the All response stabilized. A cumulative concentration response curve to All (10⁻¹⁰ to 10⁻⁷ M) was then obtained. At the conclusion of the concentration response curve, tissues were washed every 2 minutes until baseline tension was reached, then every 15 minutes for 30 minutes. Compounds were added in a volume of 10 μ l DMSO and allowed to incubate for 30 minutes before repeating the concentration response curve to All. Contractions to All were expressed as a percent of the maximum contraction obtained in the control curve (the first All concentration response curve). EC_{50} 's (concentration that contracted
50 the tissues to 1/2 the control maximum) for each curve were calculated using a 4 parameter logistics model (NonLin, SAS Institute). Potency data for each compound tested are expressed as the pA_2 (defined as -log K_B , where K_B = [molar concentration of antagonist]/([EC_{50} All with antagonist/ EC_{50} All without antagonist]-1)).

55 Using the methodology described, representative compounds of the present invention were evaluated and were found to exhibit activity as measured by a pA_2 of at least 4.1 using the rabbit aorta test system thereby demonstrating and confirming the utility of the compounds of the invention as effective angiotensin II antagonists.

Table 1

5	Example	Adrenal Glomulosa (K _I , μ m)	Rabbit Aorta (pA ₂)
	1	10.3	5.7
10	2	8.2	6.1
	3	9.6	5.4
	4	12.1	6.0
15	5	178	6.3
	6	*	6.3
	7	6.8	5.8
	8	13.0	5.8
20	9	12.4	6.6
	10	2.93	7.2
	11	*	6.7
25		*	6.6
	12	*	9.2
		*	8.2
30	13	*	7.2
		*	6.9
	14	*	7.5
		*	6.9
35	15	*	8.5
		*	7.2
	16	*	7.3
40	17	*	7.8

45

50

55

EP 0 573 271 A1

5	18	*	9.7
	19	*	8.9
	20	*	8.5
	21	*	7.2
10		*	6.3
	22	*	9.4
	23	*	8.8
	24	*	7.6
15	25	*	6.9
	26	*	8.6
	27	*	8.0
	28	*	8.7
20	29	*	7.5
	30	*	9.2
	31	*	8.9
	32	*	8.9
25	33	*	9.0
	34	*	8.5
	35	*	8.7
	36	*	9.4
30	37	*	9.4
	38	*	8.9
	39	*	9.0
	40	*	9.3
35	41	*	9.8
	42	*	8.9
	43	*	9.1
	44	*	8.3
40	45	*	9.6
	46	*	8.7
	47	*	9.0
	48	*	9.2
45	49	*	8.6
	50	*	8.7
	51	*	7.9
55			

EP 0 573 271 A1

	52	*	8.4
	53	*	8.0
5	54	*	8.6
	55	*	9.4
	56	*	7.5
10	57	*	9.5
	58	*	9.1
	59	*	9.2
15	60	*	7.8
	61	*	8.5
	62	*	9.0
	63	*	8.8
20	64	*	5.7
	65	*	8.7
	66	*	8.2
25	67	*	8.2
	68	*	9.3
	69	*	9.3
	70	*	9.3
30	71	*	7.6
	72	*	8.5
	73	*	6.8
35	74	*	7.0
	75	*	9.0
	76	*	7.5
40	77	*	8.8
	78	*	8.5
	79	*	9.3
	80	*	8.1
45	81	*	8.8
	82	*	9.5
	83	*	8.9
50	84	*	8.0
	85	*	8.9
	86	*	9.1
55			

	87	*	7.5
5	88	*	8.2
	89	*	7.5
	90	*	7.7
10	91	*	10.1
	92	*	9.9
	93	*	8.9
	94	*	9.6
15	95	*	9.8

* indicates data are not available

20

The term "pharmaceutically effective amount", as used herein, represents an amount of a compound of the invention which is capable of blocking angiotensin II receptors in mammals. The particular dose of the compound administered according to this invention will, of course, be determined by the particular circumstances surrounding the case, including the compound administered, the route of administration, the particular condition being treated, and similar considerations. The compounds can be administered by a variety of routes including the oral, rectal, transdermal, subcutaneous, intravenous, intramuscular or intranasal routes. A typical daily dose will contain from about 0.01 mg/kg to about 20 mg/kg of the active compound of this invention. Preferred daily doses will be about 0.05 to about 10 mg/kg, ideally about 0.1 to about 5 mg/kg. The term "treating," as used herein, describes the management and care of a patient for the purpose of combating the disease, condition, or disorder.

30

The term "treating" includes the administration of a compound of present invention to prevent the onset of the symptoms, alleviating the symptoms, or eliminating the disease, condition, or disorder.

25

The term "enhancing cognitive performance," as used herein, describes facilitating memory and learning in patients in need of such treatment. Examples include patients suffering from cognitive impairments like age associated mental impairment and Alzheimer's disease.

35

The compounds of Formula I are preferably formulated prior to administration. Therefore, yet another embodiment of the present invention is a pharmaceutical formulation comprising a compound of Formula I and one or more pharmaceutically acceptable carriers, diluents or excipients therefor.

40

The present pharmaceutical formulations are prepared by known procedures using well known and readily available ingredients. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semisolid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosol (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

45

Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, methyl cellulose, methyl and propylhydroxybenzoates, talc, magnesium stearate and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The compositions of the invention may be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient. The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 500 mg, more usually about 25 to about 300 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

55

The following formulation examples are illustrative only and are not intended to limit the scope of the in-

vention in any way.

Formulation 1

5

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl-4-cis-(2-naphthoxy)-L-proline	250
starch, dried	200
magnesium stearate	10
Total	460 mg

10

15

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

20

Formulation 2

A tablet is prepared using the ingredients below:

	Quantity (mg/capsule)
1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl-4-cis-((4-methylene phosphonic acid)-phenoxy)-L-proline	250
cellulose, microcrystalline	400
silicon dioxide, fumed	10
stearic acid	5
Total	665 mg

25

30

35

The components are blended and compressed to form tablets each weighing 665 mg.

Formulation 3

40

An aerosol solution is prepared containing the following components:

	Quantity (mg/capsule)
1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl-4-cis-(4-t-butyloxyphenoxy)-L-proline	0.25
ethanol	29.75
Propellant 22 (chlorodifluoromethane)	70.00
Total	100.00

45

50

The active compound is mixed with ethanol. The mixture is added to a portion of the Propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

55

Formulation 4

Tablets each containing 60 mg of active ingredient are made as follows:

EP 0 573 271 A1

	Quantity (mg/capsule)
1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl-4-cis-(4-methyl-sulfonylphenoxy)-L-proline	60 mg
starch	45 mg
microcrystalline cellulose	35 mg
polyvinylpyrrolidone (as 10% solution in water)	4 mg
sodium carboxymethyl starch	4.5 mg
magnesium stearate	0.5 mg
talco	1 mg
Total	150 mg

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation 5

Capsules each containing 80 mg of medicament are made as follows:

	Quantity (mg/capsule)
1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl-4-cis-(5-benzofuranoxo)-L-proline	80 mg
starch	59 mg
microcrystalline cellulose	59 mg
magnesium stearate	2 mg
Total	200 mg

The active ingredient, cellulose, starch and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.

Formulation 6

Suppositories each containing 225 mg of active ingredient may be made as follows:

	Quantity (mg/capsule)
1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl-4-cis-(5-benzothiophenoxy)-L-proline	225 mg
saturated fatty acid glycerides	2,000 mg
Total	2,225 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

Formulation 7

Suspensions each containing 50 mg of medicament per 5 ml dose are made as follows:

	Quantity (mg/capsule)
1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl-4-cis-(4-carboxymethylphenoxy)-L-proline	50 mg
sodium carboxymethyl cellulose	50 mg
syrup	1.25 ml
benzoic acid solution	0.10 ml
flavor	q.v.
color	q.v.
purified water to total	5 ml

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 8

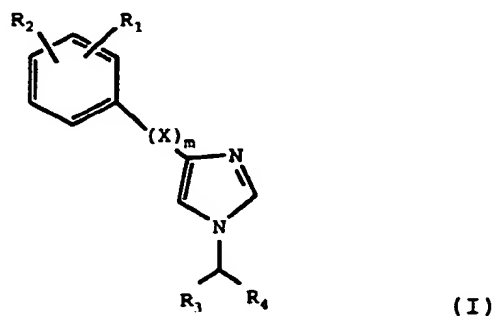
An intravenous formulation may be prepared as follows:

	Quantity (mg/capsule)
1-[1-oxo-2-[4-(2-sulfobenzoyl) amino-1H-imidazol-1-yl]octyl-4-cis-(4-hydroxyphenoxy)-L-proline	250 mg
isotonic saline	1000 mg

The solution of the above ingredients is administered intravenously at a rate of 1 ml per minute to a subject in need of treatment.

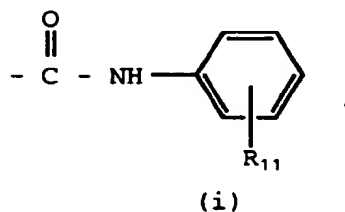
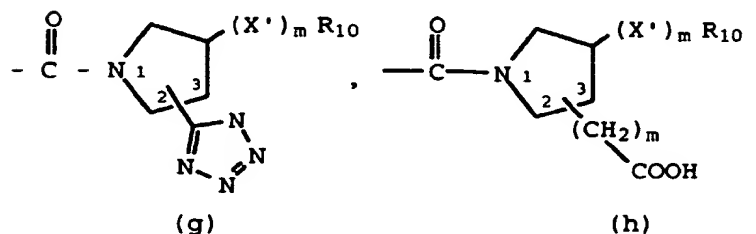
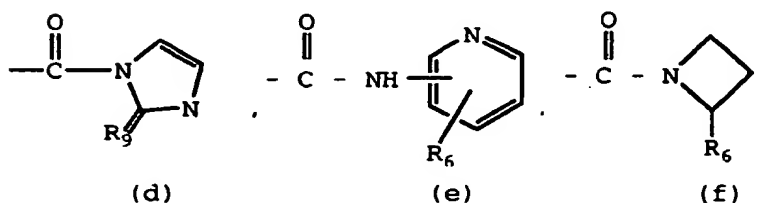
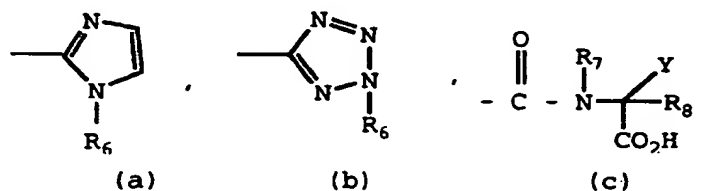
Claims

1. A compound of the formula



wherein:

R_1 is CO_2H , SO_3H , PO_3H_2 , $\text{CONHSO}_2\text{R}_6$ or 5-tetrazolyl;
 R_2 is H, -OH, -OCOCH₃, halo, C₁-C₄ alkyl, amino, acetamido, or C₁-C₄ alkyl;
 X is $-(\text{CH}_2)_m\text{NHCO}-$, $-(\text{CH}_2)_m\text{CONH}-$, $-\text{O}-$, $-\text{NH}-$, $-\text{CH}_2-$, $-(\text{CH}_2)_m\text{CO}-$, or $-\text{CO}(\text{CH}_2)_m-$;
 R_3 is C₄-C₉ straight chain alkyl, C₄-C₉ straight chain trifluoroalkyl, C₄-C₉ straight chain alkenyl, or C₄-C₉ straight chain trifluoroalkenyl;
 R_4 is $-\text{CONH}(\text{C}_1-\text{C}_4 \text{ alkyl})$, $-\text{CONH}(\text{C}_1-\text{C}_4 \text{ trifluoroalkyl})$, $-\text{CONH}(\text{hydroxy-C}_1-\text{C}_4 \text{ alkyl})$,

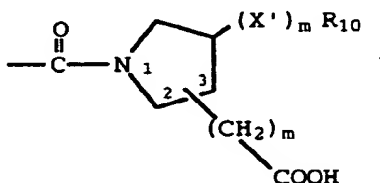


R_5 is phenyl, C₁-C₄ alkyl substituted phenyl, C₁-C₅ alkyl, or C₁-C₅ trifluoroalkyl;
 R_6 is $(\text{CH}_2)_p\text{R}_1$, or C₁-C₄ alkyl;
 R_7 is H or CH₃;
 R_8 is H or $-(\text{CH}_2)_q\text{R}_{12}$;
 R_9 is O or S;
 R_{10} is H, $-(\text{CH}_2)_p\text{R}_1$, C₁-C₇ alkyl, C₁-C₇ trifluoroalkyl, halo, substituted or unsubstituted phenyl, 3-pyridyl, 2-pyrimidyl, furanyl, oxazolyl, isoxazolyl, a substituted or unsubstituted fused bicyclic, a substituted or unsubstituted fused tricyclic, or when m is 0, 4,4-ethylenedioxy;
 R_{11} is H, OH, C₁-C₄ alkoxy, CO_2H , SO_3H , PO_3H_2 , $\text{CONHSO}_2\text{R}_6$, or tetrazolyl;
 R_{12} is OH, NH₂, or CO_2H ;
 Y is a R group of a naturally occurring amino acid;

X' is -O-, $-(CH_2)_p$ -, or -S-;
 m is independently 0 or 1;
 p is independently 0, 1, 2, 3 or 4; and
 q is 1, 2, 3, or 4;

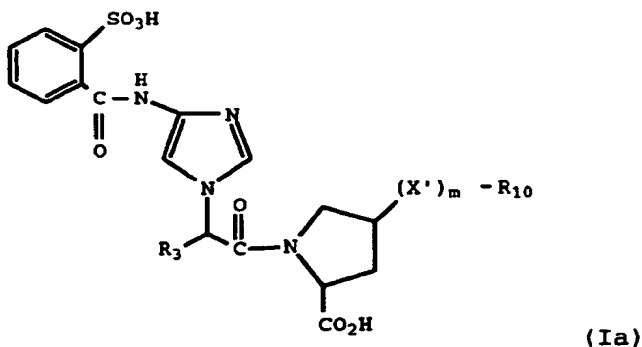
providing that when R_4 is (g) or (h), and R_{10} is not H, the carboxy of (h) or tetrazolyl of (g) is in position 2;
 and when R_4 is (g) or (h), m is 0, and R_{10} is H, the carboxy of (g) or tetrazolyl of (h) is in position 2 or 3;
 or a pharmaceutically acceptable salt or solvate thereof.

2. A compound of Claim 1 wherein R_4 is



providing that when R_{10} is not H, the carboxy is in position 2; and when m is 0, and R_{10} is H, the carboxy is in position 2 or 3.

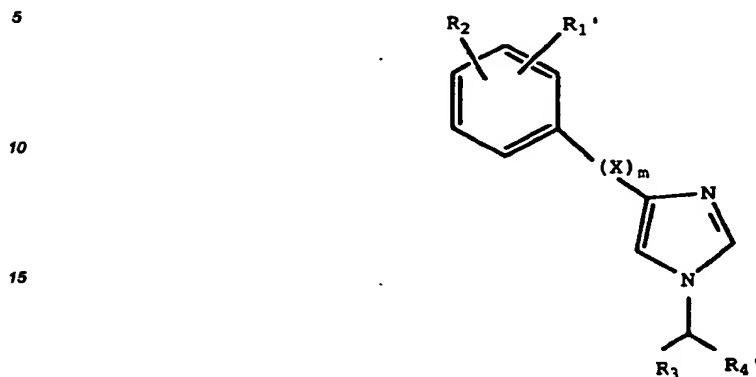
3. A compound of the formula Ia:



wherein R_3 is a C_4 - C_9 straight chain alkyl; R_{10} is an unsubstituted or para substituted phenyl, a substituted or unsubstituted fused bicyclic, or a substituted or unsubstituted fused tricyclic; m is 0 or 1; X' is -O-, -S-, or $(CH_2)_p$; and p is 0, 1, 2, 3 or 4; or a pharmaceutically acceptable salt or solvate thereof.

4. (R)-1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl-4-cis-(4-carboxymethylphenoxy)-L-proline or a pharmaceutically acceptable salt or solvate thereof.
5. (R)-1-[1-oxo-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octyl-4-cis-((4-methylene phosphonic acid)-phenoxy)-L-proline or a pharmaceutically acceptable salt or solvate thereof.
6. A compound, or a pharmaceutically acceptable salt or solvate, as claimed in any one of claims 1 to 5 for use as a pharmaceutical.
7. A compound, or a pharmaceutically acceptable salt or solvate, as claimed in any one of claims 1 to 5 for use as an antihypertension agent.
8. A pharmaceutical formulation comprising as an active ingredient a compound, or a pharmaceutically acceptable salt or solvate, as claimed in any one of claims 1 to 5, associated with one or more pharmaceutically acceptable carriers, diluents, or excipients therefor.

9. A process for preparing a compound, or a pharmaceutically acceptable salt or solvate, as claimed in any one of claims 1 to 5, which comprises hydrolyzing a compound of the formula:



wherein:

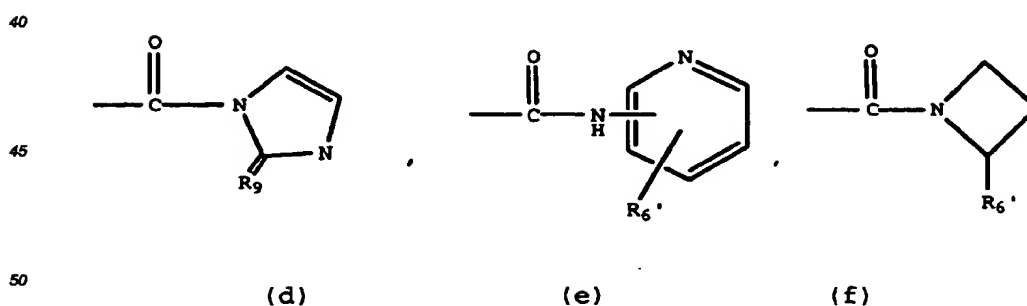
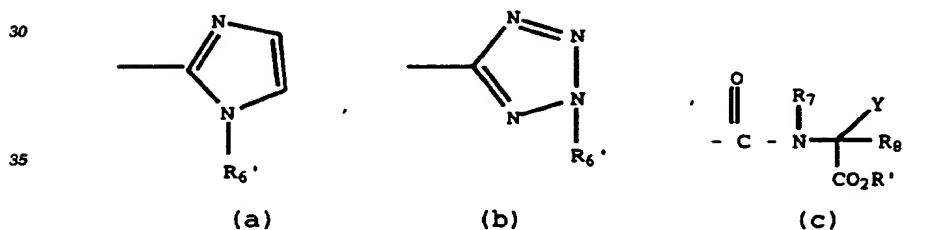
R_1' is $\text{CO}_2\text{R}'$, SO_3H , PO_3H_2 , $\text{CONHSO}_2\text{R}_6$ or 5-tetrazolyl;

R_2 is H, $-\text{OH}$, $-\text{OCOCH}_3$, halo, $\text{C}_1\text{-C}_4$ alkyl, amino, acetamido, or $\text{C}_1\text{-C}_4$ alkoxy;

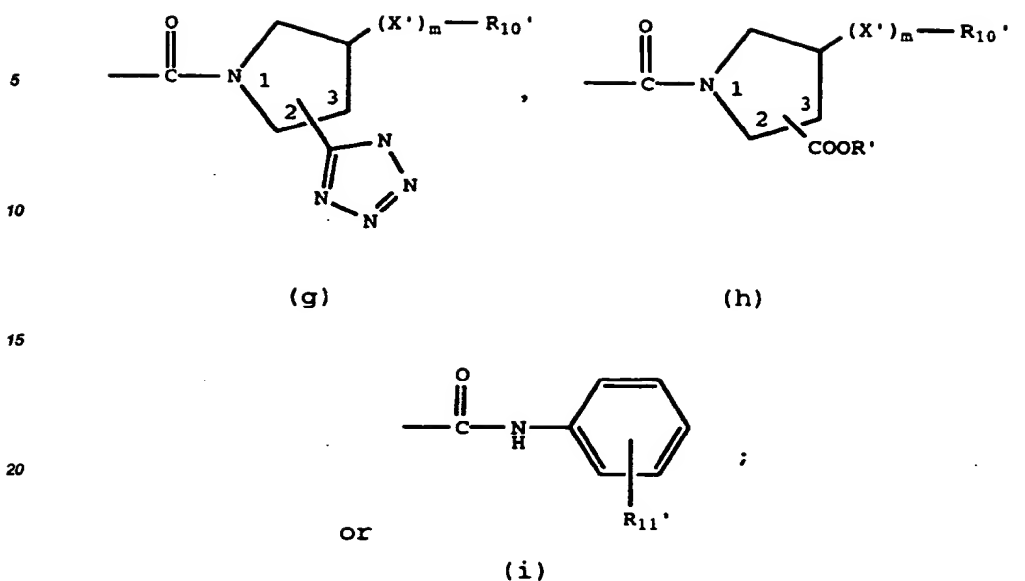
X is $-(\text{CH}_2)_m\text{NHCO}-$, $-(\text{CH}_2)_m\text{CONH}-$, $-\text{O}-$, $-\text{NH}-$, $-\text{CH}_2-$, $-(\text{CH}_2)_m\text{CO}-$, or $-\text{CO}(\text{CH}_2)_m-$;

25 R_3 is $\text{C}_4\text{-C}_9$ straight chain alkyl, $\text{C}_4\text{-C}_9$ straight chain trifluoroalkyl, $\text{C}_4\text{-C}_9$ straight chain alkenyl, or $\text{C}_4\text{-C}_9$ straight chain trifluoroalkenyl;

R_4' is $(\text{CH}_2)_p\text{R}_1'$, $-\text{CONH}(\text{C}_1\text{-C}_4 \text{ alkyl})$, $-\text{CONH}(\text{C}_1\text{-C}_4 \text{ trifluoroalkyl})$, $-\text{CONH}(\text{hydroxy-}\text{C}_1\text{-C}_4 \text{ alkyl})$,



55



R_5 is phenyl, C_1 - C_4 alkyl substituted phenyl, C_1 - C_5 alkyl, or C_1 - C_5 trifluoroalkyl;

R_6 is $(CH_2)_p R_1'$, or C_1 - C_4 alkyl;

R_7 is H or CH_3 ;

R_8 is H or $-(CH_2)_q R_{12}$;

R_9 is O or S;

R_{10}' is H, $-(CH_2)_p R_1'$, C_1 - C_7 alkyl, C_1 - C_7 trifluoroalkyl, halo, substituted or unsubstituted phenyl, 3-pyridyl, 2-pyrimidyl, furanyl, or a substituted or unsubstituted fused bicyclic ring system consisting of a benzene ring fused to a 5 or 6 member ring; providing that when R_4' is (g) or (h) and R_{10}' is not H, the ester or tetrazolyl is in position 2; and when R_4' is (g) or (h), m is 0, and R_{10}' is H, the ester or tetrazolyl is in position 2 or 3;

R_{11}' is H, OH, C_1 - C_4 alkoxy, CO_2H , SO_3R' , PO_3H_2 , $CONHSO_2R_5$, or tetrazolyl;

R_{12} is OH, NH_2 , or CO_2R' ;

Y is a R group of a naturally occurring amino acid;

X' is -O-, $(CH_2)_p$ -, or -S-;

R' is an ester group;

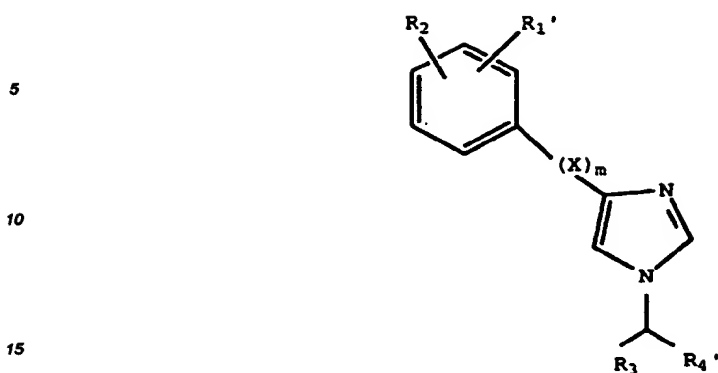
m is independently 0 or 1;

p is independently 0, 1, 2, 3 or 4; and

q is 1, 2, 3, or 4;

provided that R_1' or R_4' contains one or more $-CO_2R'$ functionalities.

10. A compound of the formula:



wherein:

R_1' is $\text{CO}_2\text{R}'$, SO_3H , PO_3H_2 , $\text{CONHSO}_2\text{R}_6$ or 5-tetrazolyl;

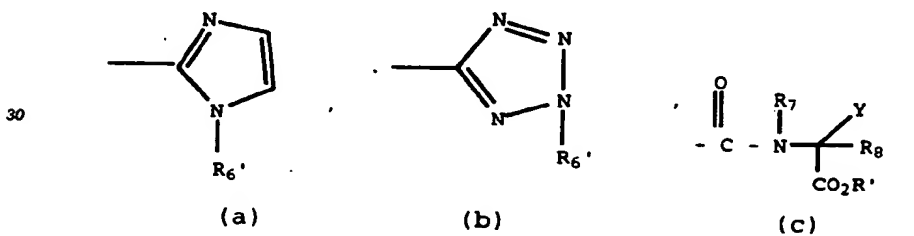
R_2 is H, -OH, -OCOCH₃, halo, C₁-C₄ alkyl, amino, acetamido, or C₁-C₄ alkoxy;

X is $-(\text{CH}_2)_m\text{NHCO}-$, $-(\text{CH}_2)_m\text{CONH}-$, $-\text{O}-$, $-\text{NH}-$, $-\text{CH}_2-$, $-(\text{CH}_2)_m\text{CO}-$, or $-\text{CO}(\text{CH}_2)_m-$;

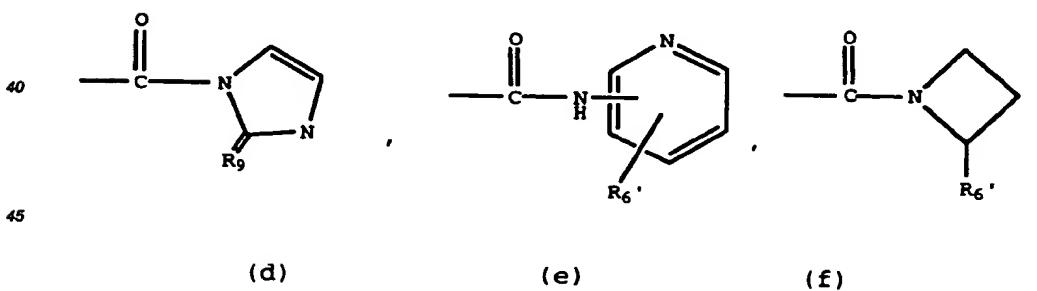
R_3 is C₄-C₉ straight chain alkyl, C₄-C₉ straight chain trifluoroalkyl, C₄-C₉ straight chain alkenyl, or C₄-C₉ straight chain trifluoroalkenyl;

R_4' is $(\text{CH}_2)_p\text{R}_1'$, $-\text{CONH}(\text{C}_1-\text{C}_4 \text{ alkyl})$, $-\text{CONH}(\text{C}_1-\text{C}_4 \text{ trifluoroalkyl})$, $-\text{CONH}(\text{hydroxy-C}_1-\text{C}_4 \text{ alkyl})$,

25



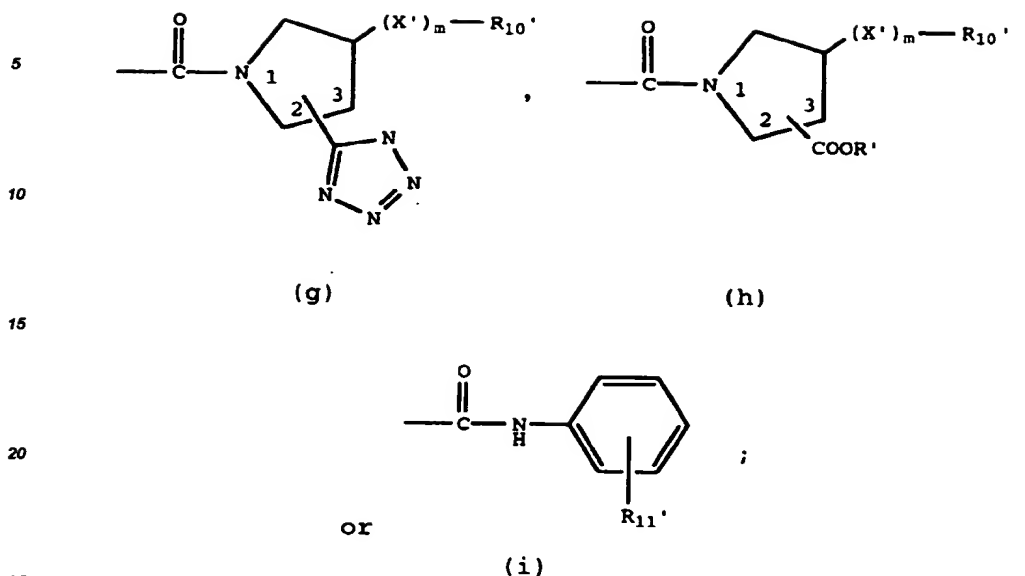
35



45

50

55



R_5 is phenyl, C_1 - C_4 alkyl substituted phenyl, C_1 - C_5 alkyl, or C_1 - C_5 trifluoroalkyl;
 R_6 is $(CH_2)_pR_1'$, or C_1 - C_4 alkyl;
 R_7 is H or CH_3 ;
 R_8 is H or $-(CH_2)_qR_{12}$;
 R_9 is O or S;
 R_{10}' is H, $-(CH_2)_pR_1'$, C_1 - C_7 alkyl, C_1 - C_7 trifluoroalkyl, halo, substituted or unsubstituted phenyl, 3-pyridyl, 2-pyrimidyl, furanyl, or a substituted or unsubstituted fused bicyclic ring system consisting of a benzene ring fused to a 5 or 6 member ring; providing that when R_4' is (g) or (h) and R_{10}' is not H, the ester or tetrazolyl is in position 2; and when R_4' is (g) or (h), m is 0, and R_{10}' is H, the ester or tetrazolyl is in position 2 or 3;
 R_{11}' is H, OH, C_1 - C_4 alkoxy, CO_2H , SO_3R' , PO_3H_2 , $CONHSO_2R_5$, or tetrazolyl;
 R_{12} is OH, NH_2 , or CO_2R' ;
Y is a R group of a naturally occurring amino acid;
 X' is -O-, $-(CH_2)_p$ -, or -S-;
 R' is an ester group;
m is independently 0 or 1;
p is independently 0, 1, 2, 3 or 4; and
q is 1, 2, 3, or 4;
provided that R_1' or R_4' contains one or more $-CO_2R'$ functionalities.

EP 0 573 271 A1



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 93 30 4264

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP-A-0 438 869 (ELI LILLY AND COMPANY) * example 50 *	1-8	C07D233/88 C07D401/06 C07D401/14 C07D403/06 C07D403/14 C07D405/14 C07D409/14 C07D413/14 A61K31/41
D	& US-A-5 073 566 ---		
A	EP-A-0 058 047 (FARMOS-YHTYMÄ OY) * abstract *	1-8	
A	EP-A-0 072 615 (FARMOS GROUP LTD.) * abstract *	1-8	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			C07D A61K
The present search report has been drawn up for all claims			
Place of search BERLIN		Date of completion of the search 16 AUGUST 1993	Examiner FRELON D. L. M. G.
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons @ : member of the same patent family, corresponding document</p>			

EPO FORM 150 (04/93) (P0401)